COMPOUNDS THAT INHIBIT MCL-1 PROTEIN

CROSS REFERENCES TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 62/479,171, filed on March 30, 2017, and U.S. Provisional Application No. 62/479,230, filed on March 30, 2017, both of which are hereby incorporated by reference in their entireties and for all purposes as if fully set forth herein.

FIELD OF THE INVENTION

The present invention relates to compounds that inhibit myeloid cell leukemia 1 protein (Mcl-1, also abbreviated as MCl-1, MCL-1 or MCL1); methods of treating diseases or conditions, such as cancer, using the compounds; and pharmaceutical compositions containing the compounds.

BACKGROUND OF THE INVENTION

One common characteristic of human cancer is overexpression of Mcl-1. Mcl-1overexpression prevents cancer cells from undergoing programmed cell death (apoptosis), allowing the cells to survive despite widespread genetic damage.

Mcl-1 is a member of the Bcl-2 family of proteins. The Bcl-2 family includes pro-apoptotic members (such as BAX and BAK) which, upon activation, form a homo-oligomer in the outer mitochondrial membrane that leads to pore formation and the escape of mitochondrial contents, a step in triggering apoptosis. Antiapoptotic members of the Bcl-2 family (such as Bcl-2, Bcl-XL, and Mcl-1) block the activity of BAX and BAK. Other proteins (such as BID, BIM, BIK, and BAD) exhibit additional regulatory functions.

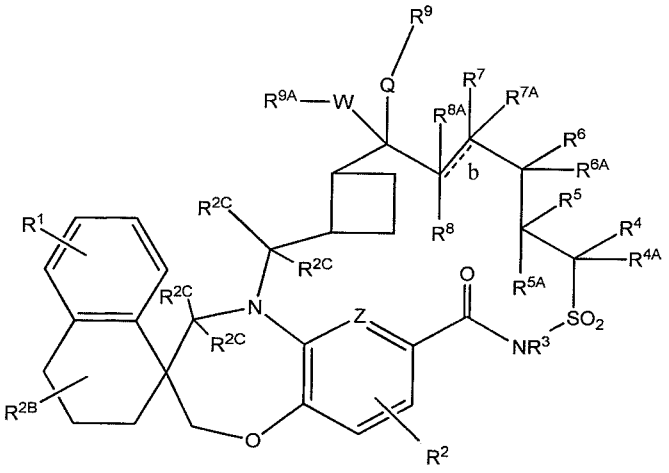
Research has shown that Mcl-1 inhibitors can be useful for the treatment of cancers. MCl-1 is overexpressed in numerous cancers. See Beroukhim et al. (2010) Nature 463, 899-90. Cancer cells containing amplifications surrounding the Mcl-1 and Bcl-2-l-1 anti-apoptotic genes depend on the expression of these

genes for survival. Beroukhim et al. Mcl-1 is a relevant target for the re-iniation of apoptosis in numerous cancer cells. See G. Lessene, P. Czabotar and P. Colman, Nat. Rev. Drug. Discov., 2008, 7, 989–1000; C. Akgul Cell. Mol. Life Sci. Vol. 66, 2009; and Arthur M. Mandelin II, Richard M. Pope, Expert Opin. Ther. Targets (2007) 11(3):363-373.

New compositions and methods for preparing and formulating Mcl-1 inhibitors would be useful.

SUMMARY

In one example, the present disclosure comprises a compound of Formula I:



(I);

a stereoisomer thereof, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of the stereoisomer thereof,

wherein:

Z is C or N;

Q is O, S, $CR^{WA}R^{WB}$, or NR^aR^b;

W is $CR^{WA}R^{WB}$, -C=O, or is absent;

R^{WA} and R^{WB} are independently selected from H, -C_{1-3}alkyl, -C_{2-3}alkenyl, -C_{2-3}alkynyl, halo, -OH, or -O-C_{1-3}alkyl;

b, represented by the symbol ------, is a single or double chemical bond which may be cis or trans;

R^1 is independently selected from H, halo, C_{1-6}alkylhalo, C_{1-6}alkyl, C_{2-6}alkenyl, $-(CH_2CH_2O)_nR^a$, $-SO_2R^a$, $-C(=O)R^a$,$-C(=O)OR^a$, or $-C(=O)NR^aR^b$;

R^2 is selected from H, halo, C_{1-6}haloalkyl, C_{1-6}alkyl, O-C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkenylene, -C_{1-6}alkyl-O-C_{1-6}alkyl, $-(CH_2CH_2O)_nR^a$, $-SO_2R^a$, $-C(=O)R^a$, $-C(=O)OR^a$, $-OC(=O)R^a$, $-C(=O)NR^aR^b$, a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, or a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl or heterocycloalkyl group have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group , and further wherein the spiroheterocycloalkyl, and heterocycloalkyl groups may include a S=O or SO_2;

R^3 is selected from H, -C_{1-6}alkylhalo, -C_{1-6}alkyl, -C_{2-6}alkenyl, $-(CH_2CH_2O)_nR^a$, $-C(=O)R^a$, $-C(=O)OR^a$, or $-C(=O)NR^aR^b$;

each of R^{2B}, R^{2C}, R^4, R^5, R^6, R^7, and R^8 is independently selected from H, halo, -C_{1-6}haloalkyl, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{1-6}alkyl-O-C_{1-6}alkyl, $-(CH_2CH_2O)_nR^a$, $-SO_2R^a$, $-C(=O)R^a$,$-C(=O)OR^a$, $-OC(=O)R^a$, $-C(=O)NR^aR^b$, a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl and heterocycloalkyl groups have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group , and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2;

alternatively R^3 and R^4 together with the atoms to which they are bonded may form a 5- to 12-membered ring, optionally containing a heteroatom selected from a N, O or S atom, in addition to the S and N atoms present in the ring, wherein the ring may optionally contain at least one double bond; and the ring may be substituted with 0, 1, 2, or 3 R^{3A} substituents;

wherein R^{3A} is selected from H, halo, -OH, C_{1-6}haloalkyl, C_{1-6}alkyl, O-C_{1-6}alkyl, C_{2-6}alkenyl, -C_{1-6}alkyl-O-C_{1-6}alkyl, -$(CH_2CH_2O)_nR^a$, -SO_2R^a, -$C(=O)R^a$,-$C(=O)OR^a$, -$OC(=O)R^a$, or -$C(=O)NR^aR^b$;

each of R^{4A}, R^{5A}, R^{6A}, R^{7A}, and R^{8A} is independently selected from H, OH, halo, or -C_{1-6}alkyl;

R^{7A} and R^{8A} are absent when b is a double chemical bond;

alternatively R^7 and R^8 together with the atoms to which they are bonded may form a 3- to 12-membered ring, wherein the ring may optionally contain at least one double bond;

R^9 is independently selected from H, OH, -(=O), -C_{1-6}haloalkyl, -C_{1-6}alkyl, -C_{1-6}alkenylene, -$(CH_2CH_2O)_nR^a$, -$C(=O)R^a$,-$C(=O)OR^a$, -$C(=O)NR^aR^b$, -C_{1-6}alkyl-O-C_{1-6}alkyl, cyano, a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl or heterocycloalkyl groups have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, and the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl group may include a C=O group, and further wherein the spiroheterocycloalkyl, and heterocycloalkyl groups may include a S=O or SO_2;

R^{9A} is independently selected from H, -OH, halo, cyano, -C_{1-6}haloalkyl, -C_{1-6}alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -C_{1-6}alkenylene, -$(CH_2CH_2O)_nR^a$, -$P(=O)OR^aOR^b$, -CSR^a, -$CS(=O)R^a$, -SR^a, -SOR^a, -OSO_2R^a, -SO_2R^a, -$(CH_2CH_2O)_nCH_3$, -(=O), -C(=O), -$C(=O)R^a$, -$C(=O)OR^a$, -$C(=O)NR^aR^b$, -CH_2-NR^aR^b, -NR^aR^b, -C_{1-6}alkyl-O-C_{1-6}alkyl, -OC_{1-6}alkyl, -O-C_{1-6}alkyl-O-C_{1-6}alkyl, phenyl, a 6- to 12-membered aryl, a 6-to 12-membered heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl and heterocycloalkyl groups have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl,

spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may contain a double bond and may contain a C=O group, and further wherein the spiroheterocycloalkyl, and heterocycloalkyl groups may include a S=O or SO_2;

wherein R^{9A} is not H when W is absent;

wherein the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, spirocycloalkyl and spiroheterocycloalkyl groups of the R^{9A} substituent can be unsubstituted or substituted with 1, 2, 3 or 4 R^{10} substituents independently selected from OH, halo, $-NR^cR^d$, $-C_{1\text{-}6}$alkyl, $-C_2$-C_6 alkenyl, $-C_2$-C_6alkynyl, $-OC_{1\text{-}6}$alkyl, $-C_{1\text{-}6}$alkyl-OH, $-C_{1\text{-}6}$alkyl-O-$C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, -O-halo$C_{1\text{-}6}$alkyl, $-SO_2R^c$, -CN, $-C(=O)NR^cR^d$, $-C(=O)R^c$, $-OC(=O)R^a$, $-C(=O)OR^c$, a 6- to 12-membered aryl, a 6- to 12-membered heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl, and heterocycloalkyl groups have 0, 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group, and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2;

alternatively R^7 and R^{9A} together with the atoms to which they are bonded may form a 3- to 12-membered ring, wherein the ring may optionally contain at least one double bond;

alternatively R^9 and R^{9A} together with Q, W, and the C to which W and Q are bonded, may form a 3- to 12-membered monocyclic or bicyclic ring, optionally containing a heteroatom in addition to Q that is selected from N, O or S, wherein the ring may contain a double bond, wherein the ring may optionally include a C=O group, and further wherein the ring optionally may be substituted by 1, 2, or 3 R^{11} substituents;

R^{11} is independently selected from H, -OH, halo, $-C_{1\text{-}6}$alkyl, $-OC_{1\text{-}6}$alkyl, $-C_{1\text{-}6}$alkyl-OH, $-C_{1\text{-}6}$alkyl-O-$C_{1\text{-}6}$alkyl, $-C_{1\text{-}6}$haloalkyl, -O-halo$C_{1\text{-}6}$alkyl, $-SO_2R^c$, -

CN, $-NR^cR^d$, $-C(=O)NR^cR^d$, $-C(=O)R^c$, $-OC(=O)R^c$, $-C(=O)OR^c$, a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl, and heterocycloalkyl groups have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl group may include a double bond, and wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl group may include a C=O group, and further wherein the spiroheterocycloalkyl, and heterocycloalkyl groups may include a S=O or SO_2;

wherein the C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl and the $-OC_{1-6}$alkyl of any of the R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{4A}, R^{5A}, R^{6A}, R^{7A}, R^{8A}, R^{9A}, R^{WA} and R^{WB} substituents is unsubstituted or substituted by 1, 2 or 3 R^{12} substituents independently selected from OH, $-OC_{1-6}$alkyl, $-C_{1-6}$alkyl-O-C_{1-6}alkyl, halo, -O-haloC_{1-6}alkyl, -CN, $-NR^aR^b$, $-(NR^aR^bR^c)_n$, $-OSO_2R^a$, $-SO_2R^a$, $-(CH_2CH_2O)_nCH_3$, -(=O), -C(=O), $-C(=O)R^a$, $-OC(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^b$, $-O-SiR^aR^bR^c$, $-SiR^aR^bR^c$, -O-(3- to 10-membered heterocycloakyl), a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl and heterocycloalkyl groups have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group, and further wherein the spiroheterocycloalkyl, and heterocycloalkyl groups may include a S=O or SO_2;

wherein the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, spirocycloalkyl and spiroheterocycloalkyl group of any of the R^2, R^4, R^5, R^6, R^7, R^8, R^9, R^{9A}, R^{10}, R^{11}, R^{12}, R^{WA} and R^{WB} substituents can be unsubstituted or substituted with 1, 2, 3 or 4 R^{13} substituents independently selected from OH, halo, $-NR^cR^d$, $-C_{1-6}$alkyl, -

OC_{1-6}alkyl, - C_{1-6}alkyl-OH, -C_{1-6}alkyl-O-C_{1-6}alkyl, C_{1-6}haloalkyl, -O-haloC_{1-6}alkyl, -SO_2R^c, -CN, -C(=O)NR^cR^d, -C(=O)R^c, -OC(=O)R^a, -C(=O)OR^c, a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl, and heterocycloalkyl groups of R^{13} have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, and spiroheterocycloalkyl groups of R^{13} or the heterocycloalkyl group of R^{13} may include a C=O group , and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2;

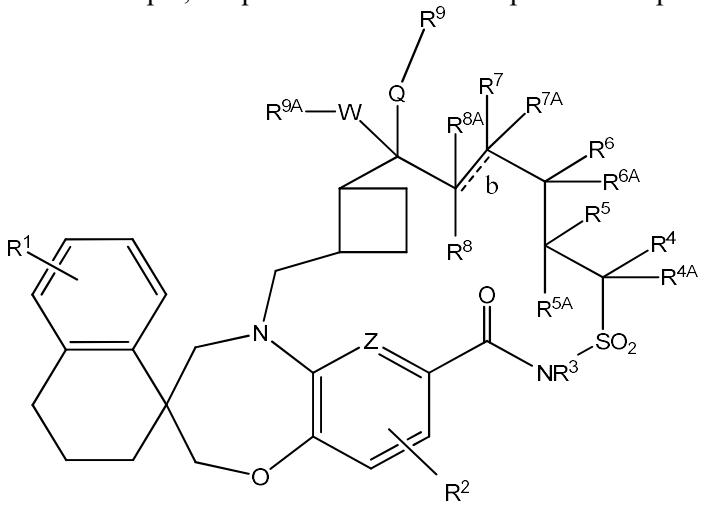
wherein each R^a, R^b, R^c, and R^d is independently hydrogen, OH, -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{1-6}alkyl-$NR^{14}R^{14}$, -$NR^{14}R^{14}$, -SO_2R^{14}, -$(CH_2CH_2O)_nCH_3$, -(=O), -C(=O)R^{14}, -OC(=O)R^{14}, -C(=O)OR^{14}, -C(=O)$NR^{14}R^{14}$, -C_{1-6}haloalkyl, -O-haloC_{1-6}alkyl, -C_{1-6}alkyl-O-C_{1-6}alkyl, benzyl, phenyl, -C_{1-6}alkyl–C(=O)OH, -C_{1-6}alkyl–C(=O)-O-C_{1-6}alkyl, -C_{1-6}alkyl–cycloalkyl, -C_{1-6}alkyl–heterocycloalkyl, -C_{1-6}alkyl– 6- to 10-membered aryl, -C_{1-6}alkyl–6- to 10-membered heteroaryl, a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, or a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, where the heteroaryl, spiroheterocycloalkyl, heterocycloalkyl group or the -C_{1-6}alkyl–heterocycloalkyl groups have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, and the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, heterocycloalkyl, group of R^a, R^b, R^c, and R^d or the heterocycloalkyl group or the -C_{1-6}alkyl–heterocycloalkyl group may include a double bond and may contain a C=O group, and the spiroheterocycloalkyl, or heterocycloalkyl may include a S=O or SO_2;

the alkyl, aryl, heteroaryl, spirocycloalkyl, spiroheterocycloalkyl, cycloalkyl, or heterocycloalkyl group of R^a, R^b, R^c, and R^d and the

heterocycloalkyl group of the -C_{1-6}alkyl–heterocycloalkyl group of R^a, R^b, R^c, and R^d can be unsubstituted or substituted with 1, 2, 3, or 4 R^{14} substituents, wherein each R^{14} is independently selected from H, -OH, -N=N=N, halo, -C_{1-6}alkyl, -C_{1-6}haloalkyl, -OC_{1-6}alkyl, -C_{1-6}alkyl-O-C_{1-6}alkyl, -C_{1-6}haloalkyl, -O-haloC_{1-6}alkyl, phenyl, tolyl, -C(=O)C_{1-6}alkyl, -C(=O)O-C_{1-6}alkyl, $N(CH_3)_2$ or -SO_2-$N(CH_3)_2$; and

wherein n is independently in each instance an integer of 1, 2, 3 or 4.

In one example, the present disclosure comprises a compound of Formula I':



(I');

a stereoisomer thereof, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of the stereoisomer thereof,

wherein:

Z is C or N;

Q is O or S;

W is $CR^{WA}R^{WB}$ or C=O;

R^{WA} and R^{WB} are independently selected from H, C_{1-3}alkyl, halo, -OH, or -O-C_{1-3}alkyl;

b, represented by the symbol ------ is a single or double chemical bond which may be cis or trans;

R^1 is independently selected from H, halo, C_{1-6}alkylhalo, C_{1-6}alkyl, -$(CH_2CH_2O)_nR^a$, -SO_2R^a, -C(=O)R^a ,-C(=O)OR^a, or -C(=O)NR^aR^b;

R^2 is selected from H, halo, -C_{1-6}haloalkyl, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{1-6}alkyl-O-C_{1-6}alkyl, -$(CH_2CH_2O)_nR^a$, -SO_2R^a, -C(=O)R^a , -C(=O)OR^a, -OC(=O)R^a, or -C(=O)NR^aR^b,

R^3 is independently selected from H, -C_{1-6}alkylhalo, -C_{1-6}alkyl, -C_{2-6} alkenyl, -$(CH_2CH_2O)_nR^a$, -C(=O)R^a ,-C(=O)OR^a, or -C(=O)NR^aR^b;

each of R^4, R^5, R^6, R^7, and R^8 is independently selected from H, halo, -C_{1-6}haloalkyl, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{1-6}alkyl-O-C_{1-6}alkyl, -$(CH_2CH_2O)_nR^a$, -SO_2R^a, -C(=O)R^a ,-C(=O)OR^a, -OC(=O)R^a, -C(=O)NR^aR^b, a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl,a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl and heterocycloalkyl groups have 1, 2, 3, or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group , and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2;

alternatively R^3 and R^4 together with the atoms to which they are bonded may form a 5- to 12-membered ring, optionally containing a heteroatom selected from a N, O or S atom, in addition to the S and N atoms present in the ring, wherein the ring may optionally contain at least one double bond; and the ring may be substituted with 0, 1, 2, or 3 R^{3A} substituents;

R^{3A} is independently selected from H, halo, -OH, C_{1-6}haloalkyl, C_{1-6}alkyl, O-C_{1-6}alkyl, C_{2-6}alkenyl, -C_{1-6}alkyl-O-C_{1-6}alkyl, -$(CH_2CH_2O)_nR^a$, -SO_2R^a, -$C(=O)R^a$,-$C(=O)OR^a$, -$OC(=O)R^a$, -$C(=O)NR^aR^b$;

each of R^{4A}, R^{5A}, R^{6A}, R^{7A}, and R^{8A} is independently selected from H, OH, halo, -C_{1-6}alkyl;

R^{7A} and R^{8A} are absent when b is a double chemical bond;

R^9 is independently selected from H, -C_{1-6}haloalkyl, -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -$(CH_2CH_2O)_nR^a$, -$C(=O)R^a$,-$C(=O)OR^a$, -$C(=O)NR^aR^b$, -C_{1-6}alkyl-O-C_{1-6}alkyl, a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl and heterocycloalkyl groups have 1, 2, 3, or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group, and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2;

R^{9A} is independently selected from H, C_{1-6}haloalkyl, C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -$(CH_2CH_2O)_nR^a$, -SO_2R^a, -$C(=O)R^a$,-$C(=O)OR^a$, -$C(=O)NR^aR^b$, -NR^aR^b, -N=N=N, -C_{1-6}alkyl-O-C_{1-6}alkyl, a 6- to 12-membered aryl, a 6- to 12-membered heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl and heterocycloalkyl groups have 1, 2, 3, or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group, and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2;

wherein the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, spirocycloalkyl and spiroheterocycloalkyl groups of the R^{9A} substituent can be unsubstituted or substituted with 1, 2, 3 or 4 R^{10} substituents independently selected from OH, halo, -NR^cR^d, -C_{1-6}alkyl, -C_2-C_6 alkenyl, -C_2-C_6alkynyl, -OC_{1-6}alkyl, -C_{1-6}alkyl-OH, -C_{1-6}alkyl-O-C_{1-6}alkyl, C_{1-6}haloalkyl, -O-haloC_{1-6}alkyl, -SO_2R^c, -CN, -$C(=O)NR^cR^d$, -$C(=O)R^c$, -$OC(=O)R^a$, -$C(=O)OR^c$, a 6- to 12-membered aryl, a 6- to 12-membered heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl, and heterocycloalkyl groups have 0, 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group, and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2;

alternatively R^9 and R^{9A} together with Q, W, and the C to which W and Q are bonded, may form a 3- to 12-membered monocyclic or bicyclic ring, optionally containing a heteroatom in addition to Q that is selected from N, O or S, wherein the ring

may contain a double bond, wherein the ring may optionally include a C=O group, and further wherein the ring optionally may be substituted by 1, 2, or 3 R^{11} substituents;

R^{11} is independently selected from OH, halo, $-NR^cR^d$, $-C_{1-6}$alkyl, $-OC_{1-6}$alkyl, $-C_{1-6}$alkyl-OH, $-C_{1-6}$alkyl-O-C_{1-6}alkyl, C_{1-6}haloalkyl, -O-haloC_{1-6}alkyl, $-SO_2R^c$, -CN, $-C(=O)NR^cR^d$, $-C(=O)R^c$, $-OC(=O)R^a$, $-C(=O)OR^c$, a 6- to 12-membered aryl or heteroaryl, a 6- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl, and heterocycloalkyl group have 1, 2, 3, or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group, and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2;

wherein the $-C_{1-6}$alkyl of any of the R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{4A}, R^{5A}, R^{6A}, R^{7A}, R^{8A}, and R^{9A} substituents is unsubstituted or substituted by 1, 2 or 3 R^{12} substituents independently selected from OH, $-OC_{1-6}$alkyl, $-C_{1-6}$alkyl-O-C_{1-6}alkyl, halo, -O-haloC_{1-6}alkyl, -CN, $-NR^aR^b$, $-(NR^aR^bR^c)_n$, $-SO_2R^a$, $-(CH_2CH_2O)_nCH_3$, (=O), -C(=O), $-C(=O)R^a$, $-OC(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^b$, $-O-SiR^aR^bR^c$, -O-(3- to 12-membered heterocycloakyl), phenyl, a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl and heterocycloalkyl groups have 1, 2, 3, or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group , and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2;

wherein the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, spirocycloalkyl and spiroheterocycloalkyl groups of any of the R^2, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11} and R^{12} substituents can be unsubstituted or substituted with 1, 2, 3 or 4 R^{13} substituents independently selected from OH, halo, $-C_{1-6}$alkyl, $-OC_{1-6}$alkyl, $-C_{1-6}$alkyl-OH, $-C_{1-6}$alkyl-O-C_{1-6}alkyl, C_{1-6}haloalkyl, -O-haloC_{1-6}alkyl, $-SO_2R^c$, $-NR^cR^d$, -CN, $-C(=O)NR^cR^d$, $-C(=O)R^c$, $-OC(=O)R^a$, $-C(=O)OR^c$, $-B(OH)_2$, a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl, and heterocycloalkyl groups have 1, 2, 3, or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group , and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2;

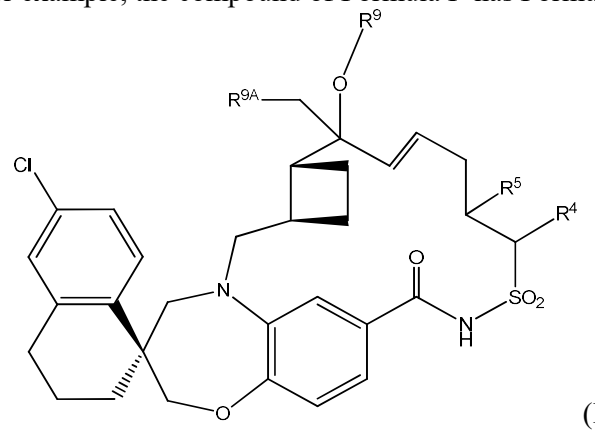
wherein each R^a, R^b, R^c, and R^d is independently H, OH, $-C_{1-6}$alkyl, $-C_{1-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{1-6}$alkyl-$NR^{14}R^{14}$, $NR^{14}R^{14}$, $-SO_2R^{14}$, $-(CH_2CH_2O)_nCH_3$, (=O), $-C(=O)R^{14}$, $-OC(=O)R^{14}$, $-C(=O)OR^{14}$, $-C(=O)NR^{14}R^{14}$, C_{1-6}haloalkyl, -O-haloC_{1-6}alkyl, $-C_{1-6}$alkyl-O-C_{1-6}alkyl, $-C_{1-6}$alkyl-OH, benzyl, phenyl, a $-C_{1-6}$alkyl–3- to 12-membered heterocycloalkyl, a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl, and heterocycloalkyl groups and the heterocycloalkyl group of the $-C_{1-6}$alkyl–heterocycloalkyl

group have 1, 2, 3, or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, heterocycloalkyl, and the heterocycloalkyl groups of the -C_{1-6}alkyl–heterocycloalkyl group may include a C=O group, and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2;

the alkyl, aryl, heteroaryl, spirocycloalkyl, spiroheterocycloalkyl, cycloalkyl, heterocycloalkyl and the heterocycloalkyl groups of the -C_{1-6}alkyl–heterocycloalkyl groups of R^a, R^b, R^c, and R^d can be unsubstituted or substituted with 1, 2, 3, or 4 R^{14} substituents independently selected from H, OH, -N=N=N, halo, -C_{1-6}alkyl, -OC_{1-6}alkyl, C_{1-6}haloalkyl, -O-haloC_{1-6}alkyl, phenyl, tolyl, -C(O)C_{1-6}alkyl, -C(O)OCH_3, SO_2-phenyl, or -SO_2-N$(CH_3)_2$; and

n is independently, in each instance, an integer of 1, 2, 3 or 4.

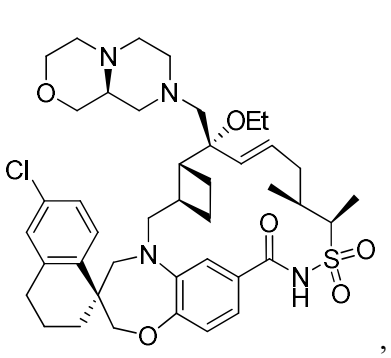
In another example, the compound of Formula I' has Formula II'a:



(II'a)

or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof.

In one aspect, the present disclosure provides a compound selected from:



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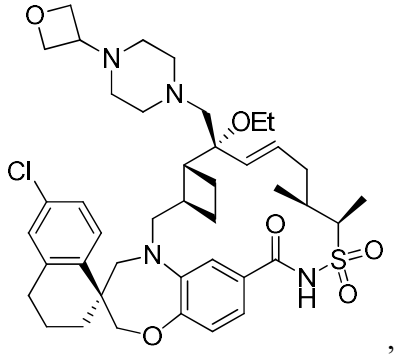

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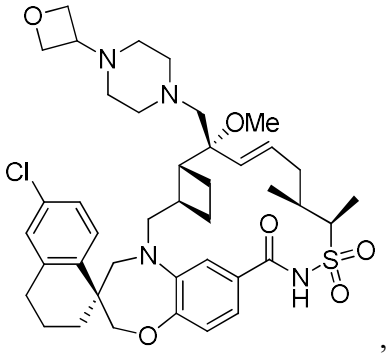

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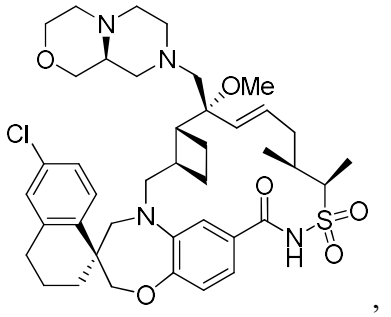

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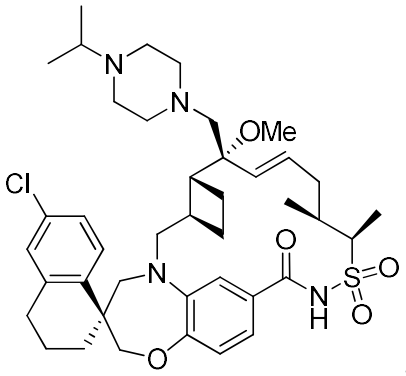
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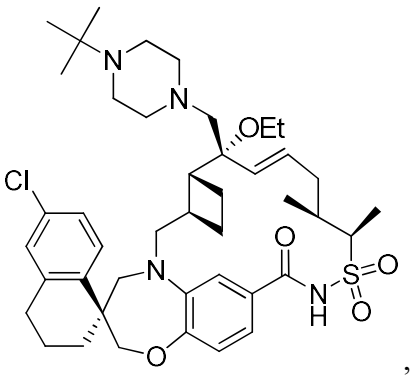
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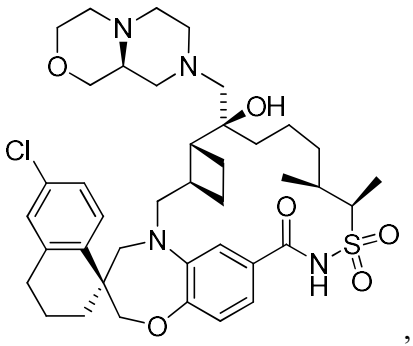
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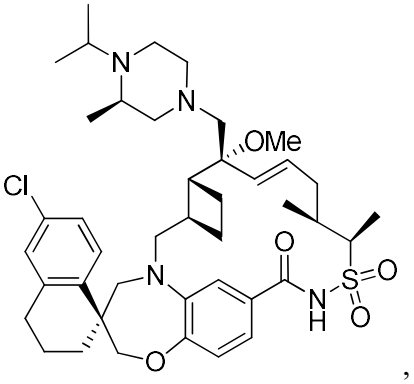
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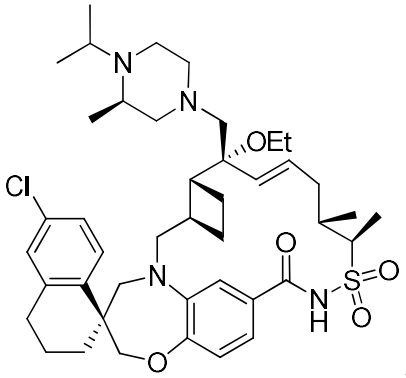
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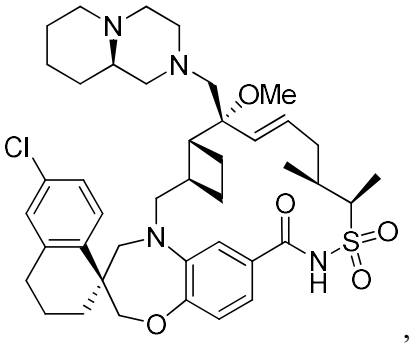
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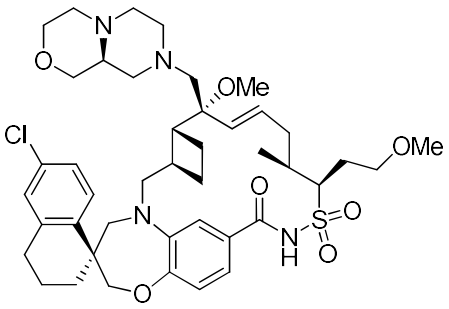
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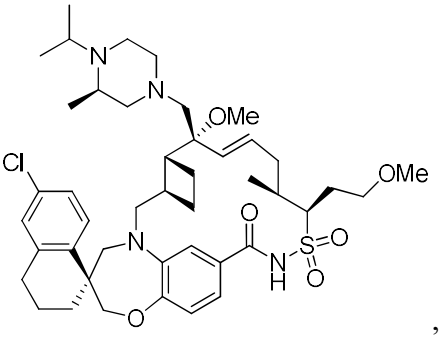
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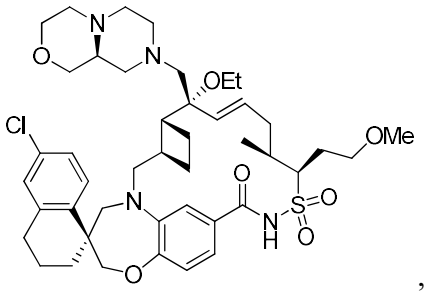
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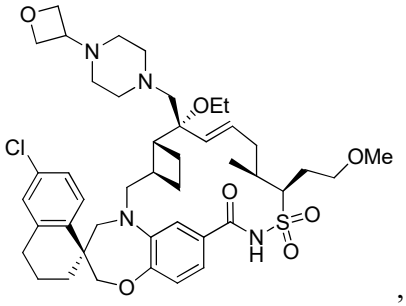
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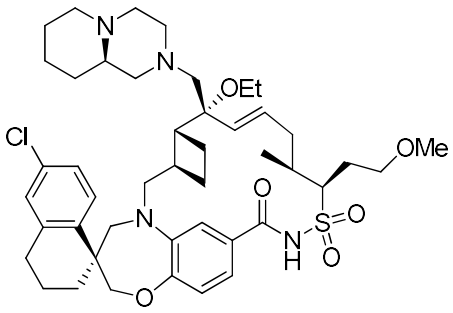
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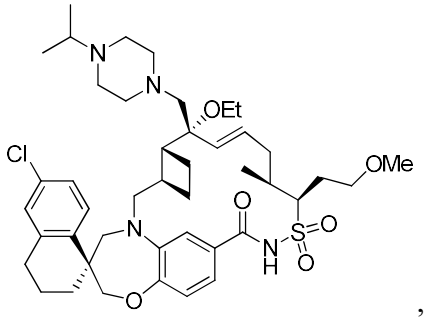
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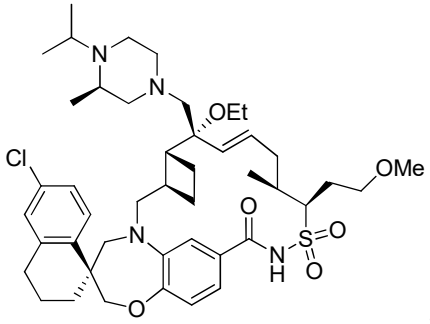
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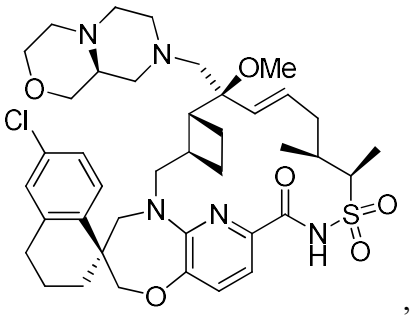
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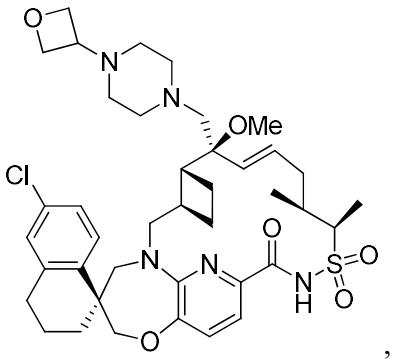
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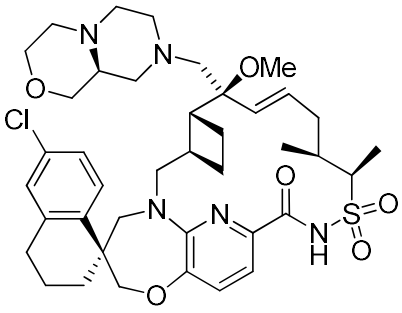
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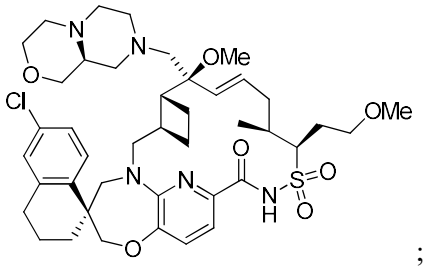
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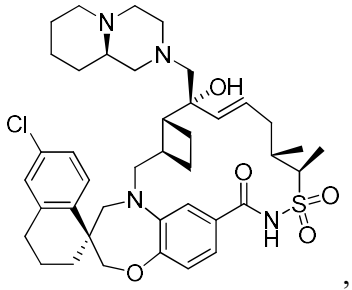
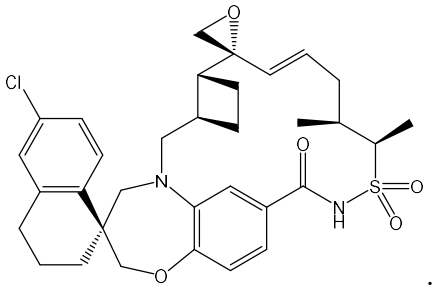
or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof.

In another aspect, the present disclosure provides a compound, wherein the compound is



, or is the pharmaceutically acceptable salt thereof.

In yet another aspect, the present disclosure provides a compound, wherein the compound is



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Another aspect of the present disclosure provides a pharmaceutical composition that comprises the compound of any of the examples or the pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

In another aspect, the present disclosure refers to the use of a compound as described herein in the preparation of a medicament for treating cancer.

Another example of the present disclosure provides a method of treating cancer. Such methods include: administering to a patient in need thereof a therapeutically effective amount of the compound of any of the examples or a pharmaceutically acceptable salt thereof. In some such methods, the cancer is a hematologic malignancy. In some such methods, the cancer is selected from the group consisting of breast cancer, colorectal cancer, skin cancer, melanoma, ovarian cancer, kidney cancer, lung cancer, non-small cell lung cancer, lymphoma, non-Hodgkin's lymphoma, myeloma, multiple myeloma, leukemia, and acute myelogenous leukemia. In some other such methods, the cancer is multiple myeloma. In some other such methods, the cancer is acute myelogenous leukemia. In some other such methods, the cancer is non-Hodgkin's lymphoma. In another example, the method further includes administering to a patient in need thereof a therapeutically effective amount of an additional pharmaceutically active compound. For example, in some such methods the additional pharmaceutically active compound is carfilzomib. In others, the additional pharmaceutically active compound is venetoclax. In still other such methods, the additional pharmaceutically active compound is cytarabine.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Methods and materials are described herein for use in the present disclosure; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present

specification, including definitions, will control.

Other features and advantages of the disclosure will be apparent from the following detailed description and figures, and from the Claims.

BRIEF DESCRIPTION OF DRAWINGS

Figure 1 demonstrates the superior in vivo efficacy of Example 1 relative to Reference Compound 1 in a tumor PD model. Both compounds were dosed orally to female athymic nude mice inoculated with OPM-2 Luc cells.

Figure 2 demonstrates the superior in vivo efficacy of Example 2 and Example 3 relative to Reference Compound 1 in a tumor PD model. Both compounds were dosed orally to female athymic nude mice inoculated with OPM-2 Luc cells.

Figure 3 demonstrates the superior in vivo efficacy of Example 4 relative to Reference Compound 1 in a tumor PD model. Both compounds were dosed orally to female athymic nude mice inoculated with OPM-2 Luc cells.

Figure 4 demonstrates the superior in vivo efficacy of Example 10 relative to Reference Compound 1 in a tumor PD model. Both compounds were dosed orally to female athymic nude mice inoculated with OPM-2 Luc cells.

Figure 5 demonstrates the superior in vivo efficacy of Example 11 relative to Reference Compound 1 in a tumor PD model. Both compounds were dosed orally to female athymic nude mice inoculated with OPM-2 Luc cells.

Figure 6 demonstrates the superior in vivo efficacy of Example 13 and Example 14 relative to Reference Compound 1 in a tumor PD model. Both compounds were dosed orally to female athymic nude mice inoculated with OPM-2 Luc cells.

Figure 7 demonstrates the superior in vivo efficacy of Example 18 relative to Reference Compound 1 in a tumor PD model. Both compounds were dosed orally to female athymic nude mice inoculated with OPM-2 Luc cells.

Figure 8 demonstrates in vivo efficacy of Example 1 in an OPM-2 xenograft efficacy model. Example 1 was dosed orally to female athymic nude mice inoculated with OPM-2 Luc cells.

Figure 9 demonstrates in vivo efficacy of Example 4 in an OPM-2 xenograft efficacy model. Example 1 was dosed orally to female athymic nude mice inoculated with OPM-2 Luc cells.

Figure 10 demonstrates in vivo efficacy of Example 10 in an OPM-2 xenograft efficacy model. Example 1 was dosed orally to female athymic nude mice inoculated with OPM-2 Luc cells.

Figure 11 demonstrates in vivo efficacy of Example 11 in an OPM-2 xenograft efficacy model. Example 1 was dosed orally to female athymic nude mice inoculated with OPM-2 Luc cells.

Figure 12 demonstrates in vivo efficacy of Example 13 in an OPM-2 xenograft efficacy model. Example 1 was dosed orally to female athymic nude mice inoculated with OPM-2 Luc cells.

Figure 13 demonstrates in vivo efficacy of Example 18 in an OPM-2 xenograft efficacy model. Example 1 was dosed orally to female athymic nude mice inoculated with OPM-2 Luc cells.

DETAILED DESCRIPTION

The symbol "–" represents a covalent bond and can also be used in a radical group to indicate the point of attachment to another group. In chemical structures, the symbol – is commonly used to represent a methyl group in a molecule.

As used herein, chemical structures which contain one or more stereocenters depicted with dashed and bold bonds (i.e., ····· and ▬) are meant to indicate absolute stereochemistry of the stereocenter(s) present in the chemical structure. As used herein, bonds symbolized by a simple line do not indicate a stereo-preference. Unless otherwise indicated to the contrary, chemical structures that include one or more stereocenters which are illustrated herein without indicating absolute or relative stereochemistry encompass all possible stereoisomeric forms of the compound (e.g., diastereomers, enantiomers) and

mixtures thereof. Structures with a single bold or dashed line, and at least one additional simple line, encompass a single enantiomeric series of all possible diastereomers.

As used herein, the term "about" is meant to account for variations due to experimental error. All measurements reported herein are understood to be modified by the term "about," whether or not the term is explicitly used, unless explicitly stated otherwise. As used herein, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise.

The term "alkyl" means a straight or branched chain hydrocarbon. Representative examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, sec-butyl, pentyl and hexyl. Typical alkyl groups are alkyl groups having from 1 to 8 carbon atoms, which groups are commonly represented as C_{1-8} alkyl.

The term "compound", as used herein is meant to include all stereoisomers, geometric isomers, tautomers, and isotopes of the structures depicted. Compounds herein identified by name or structure as one particular tautomeric form are intended to include other tautomeric forms unless otherwise specified.

All compounds, and pharmaceutically acceptable salts thereof, can be found together with other substances such as water and solvents (e.g., hydrates and solvates).

The term "cycloalkyl" means a cyclic, nonaromatic hydrocarbon. Representative examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. A cycloalkyl group can contain one or more double bonds. Representative examples of cycloalkyl groups that contain double bonds include cyclopentenyl, cyclohexenyl, cyclohexadienyl and cyclobutadienyl. Common cycloalkyl groups are C_{3-8} cycloalkyl groups.

The term "excipient", as used herein, means any pharmaceutically acceptable additive, carrier, diluent, adjuvant or other ingredient, other than the active pharmaceutical ingredient (API), which is typically included for formulation and/or administration to a patient. Handbook of Pharmaceutical

Excipients, 5th Edition, R.C. Rowe , P.J. Sheskey, and S.C. Owen, editors, Pharmaceutical Press, 2005, Hardback, 928, 0853696187.

For the terms "for example" and "such as" and grammatical equivalences thereof, the phrase "and without limitation" is understood to follow unless explicitly stated otherwise.

The term "halogen" or "halo" means F, Cl, Br or I.

The term "patient" means subjects including animals, such as dogs, cats, cows, horses, sheep and humans. Particular patients are mammals. The term patient includes males and females.

The term "patient in need" means a patient having, or at risk of having, one or more diseases or conditions where the Mcl-1 protein is involved, such as cancers. Identifying a patient in need can be in the judgment of a subject or a health care professional and can be subjective (e.g., opinion) or objective (e.g., measurable by a test or diagnostic method).

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrastemal injection, and infusion.

Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions, or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents, or vehicles include water, ethanol, polyols (propylene glycol, polyethylene glycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

The term "pharmaceutically acceptable" is employed herein to refer to those ligands, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for administration to a patient, commensurate with a reasonable benefit/risk ratio.

The phrase "pharmaceutically acceptable carrier" as used herein means a pharmaceutically acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material. As used herein the language "pharmaceutically acceptable carrier" includes buffer, sterile water for injection, solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose, and sucrose; (2) starches, such as corn starch, potato starch, and substituted or unsubstituted β-cyclodextrin; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil, and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol, and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations. In certain Claims, pharmaceutical compositions provided herein are non-pyrogenic, i.e., do not induce significant temperature elevations when administered to a patient.

The term "pharmaceutically acceptable salt" refers to the relatively non-toxic, inorganic and organic acid addition salts of a compound provided herein. These salts can be prepared *in situ* during the final isolation and purification of a

compound provided herein, or by separately reacting the compound in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, laurylsulphonate salts, and amino acid salts, and the like. (See, for example, Berge et al. (1977) "Pharmaceutical Salts", *J. Pharm. Sci.* 66: 1-19).

The phrases "systemic administration", "administered systemically", "peripheral administration", and "administered peripherally" as used herein mean the administration of a ligand, drug, or other material via route other than directly into the central nervous system, such that it enters the patient's system and thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

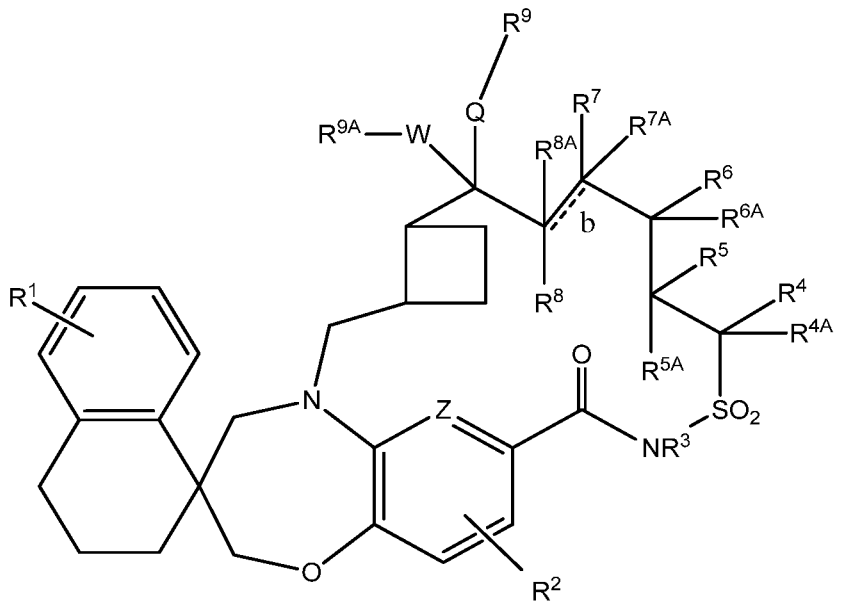
The term "therapeutically effective amount" means an amount of a compound that ameliorates, attenuates or eliminates one or more symptom of a particular disease or condition, or prevents or delays the onset of one of more symptom of a particular disease or condition.

The terms "treating", "treat" or "treatment" and the like include preventative (e.g., prophylactic) and palliative treatment.

EMBODIMENTS A

The embodiments listed below are presented in numbered form for convenience and for ease and clarity of reference in referring back to multiple embodiments.

In a first embodiment, the present invention comprises a compound of Formula I':



(I');

a stereoisomer thereof, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of the stereoisomer thereof,

wherein:

Z is C or N;

Q is O or S;

W is $CR^{WA}R^{WB}$ or C=O;

R^{WA} and R^{WB} are independently selected from H, C_{1-3}alkyl, halo, -OH, or -O-C_{1-3}alkyl;

b, represented by the symbol ------ is a single or double chemical bond which may be cis or trans;

R^1 is independently selected from H, halo, C_{1-6}alkylhalo, C_{1-6}alkyl, -$(CH_2CH_2O)_nR^a$, -SO_2R^a, -C(=O)R^a ,-C(=O)OR^a, or -C(=O)NR^aR^b;

R^2 is selected from H, halo, -C_{1-6}haloalkyl, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{1-6}alkyl-O-C_{1-6}alkyl, -$(CH_2CH_2O)_nR^a$, -SO_2R^a, -C(=O)R^a , -C(=O)OR^a, -OC(=O)R^a, or -C(=O)NR^aR^b,

R^3 is independently selected from H, -C_{1-6}alkylhalo, -C_{1-6}alkyl, -C_{2-6} alkenyl, -$(CH_2CH_2O)_nR^a$, -C(=O)R^a ,-C(=O)OR^a, or -C(=O)NR^aR^b;

each of R^4, R^5, R^6, R^7, and R^8 is independently selected from H, halo, -C_{1-6}haloalkyl, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{1-6}alkyl-O-C_{1-6}alkyl, -$(CH_2CH_2O)_nR^a$, -SO_2R^a, -C(=O)R^a ,-C(=O)OR^a, -OC(=O)R^a, -C(=O)N$R^a R^b$, a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl,a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl and heterocycloalkyl groups have 1, 2, 3, or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group , and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2;

alternatively R^3 and R^4 together with the atoms to which they are bonded may form a 5- to 12-membered ring, optionally containing a heteroatom selected from a N, O or S atom, in addition to the S and N atoms present in the ring, wherein the ring may optionally contain at least one double bond; and the ring may be substituted with 0, 1, 2, or 3 R^{3A} substituents;

R^{3A} is independently selected from H, halo, -OH, C_{1-6}haloalkyl, C_{1-6}alkyl, O-C_{1-6}alkyl, C_{2-6}alkenyl, -C_{1-6}alkyl-O-C_{1-6}alkyl, -$(CH_2CH_2O)_nR^a$, -SO_2R^a, -C(=O)R^a ,-C(=O)OR^a, -OC(=O)R^a, -C(=O)N$R^a R^b$;

each of R^{4A}, R^{5A}, R^{6A}, R^{7A}, and R^{8A} is independently selected from H, OH, halo, -C_{1-6}alkyl;

R^{7A} and R^{8A} are absent when b is a double chemical bond;

R^9 is independently selected from H, -C_{1-6}haloalkyl, -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -$(CH_2CH_2O)_nR^a$, -C(=O)R^a ,-C(=O)OR^a, -C(=O)N$R^a R^b$, -C_{1-6}alkyl-O-C_{1-6}alkyl, a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl andheterocycloalkyl groups have 1, 2, 3, or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a

C=O group, and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2;

R^{9A} is independently selected from H, C_{1-6}haloalkyl, C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -$(CH_2CH_2O)_nR^a$, -SO_2R^a, -$C(=O)R^a$,-$C(=O)OR^a$, -$C(=O)NR^aR^b$, -NR^aR^b, -N=N=N, -C_{1-6}alkyl-O-C_{1-6}alkyl, a 6- to 12-membered aryl, a 6- to 12-membered heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl and heterocycloalkyl groups have 1, 2, 3, or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group, and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2;

wherein the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, spirocycloalkyl and spiroheterocycloalkyl groups of the R^{9A} substituent can be unsubstituted or substituted with 1, 2, 3 or 4 R^{10} substituents independently selected from OH, halo, -NR^cR^d, -C_{1-6}alkyl, -C_2-C_6 alkenyl, -C_2-C_6alkynyl, -OC_{1-6}alkyl, -C_{1-6}alkyl-OH, -C_{1-6}alkyl-O-C_{1-6}alkyl, C_{1-6}haloalkyl, -O-haloC_{1-6}alkyl, -SO_2R^c, -CN, -$C(=O)NR^cR^d$, -$C(=O)R^c$, -$OC(=O)R^a$, -$C(=O)OR^c$, a 6- to 12-membered aryl, a 6- to 12-membered heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl, and heterocycloalkyl groups have 0, 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group, and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2;

alternatively R^9 and R^{9A} together with Q, W, and the C to which W and Q are bonded, may form a 3- to 12-membered monocyclic or bicyclic ring, optionally containing a heteroatom in addition to Q that is selected from N, O or

S, wherein the ring may contain a double bond, wherein the ring may optionally include a C=O group, and further wherein the ring optionally may be substituted by 1, 2, or 3 R^{11} substituents;

R^{11} is independently selected from OH, halo, $-NR^cR^d$, $-C_{1-6}$alkyl, $-OC_{1-6}$alkyl, $-C_{1-6}$alkyl-OH, $-C_{1-6}$alkyl-O-C_{1-6}alkyl, C_{1-6}haloalkyl, -O-haloC_{1-6}alkyl, $-SO_2R^c$, -CN, $-C(=O)NR^cR^d$, $-C(=O)R^c$, $-OC(=O)R^a$, $-C(=O)OR^c$, a 6- to 12-membered aryl or heteroaryl, a 6- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl, and heterocycloalkyl group have 1, 2, 3, or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group, and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2;

wherein the $-C_{1-6}$alkyl of any of the R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{4A}, R^{5A}, R^{6A}, R^{7A}, R^{8A}, and R^{9A} substituents is unsubstituted or substituted by 1, 2 or 3 R^{12} substituents independently selected from OH, $-OC_{1-6}$alkyl, $-C_{1-6}$alkyl-O-C_{1-6}alkyl, halo, -O-haloC_{1-6}alkyl, -CN, $-NR^aR^b$, $-(NR^aR^bR^c)_n$, $-SO_2R^a$, $-(CH_2CH_2O)_nCH_3$, (=O), -C(=O), $-C(=O)R^a$, $-OC(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^b$, $-O-SiR^aR^bR^c$, -O-(3- to 12-membered heterocycloakyl), phenyl, a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl and heterocycloalkyl groups have 1, 2, 3, or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group , and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2;

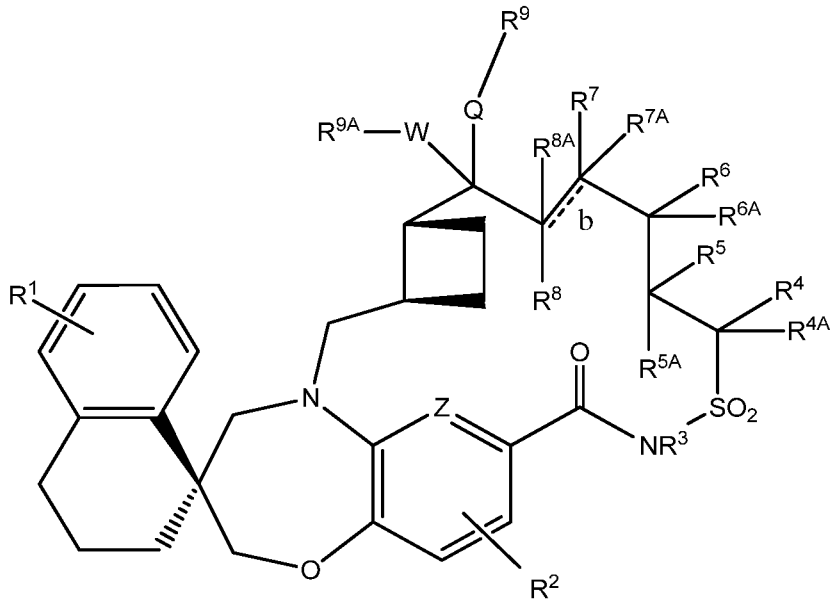
wherein the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, spirocycloalkyl and spiroheterocycloalkyl groups of any of the R^2, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11} and R^{12} substituents can be unsubstituted or substituted with 1, 2, 3 or 4 R^{13} substituents independently selected from OH, halo, -C_{1-6}alkyl, -OC_{1-6}alkyl, - C_{1-6}alkyl-OH, - C_{1-6}alkyl-O-C_{1-6}alkyl, C_{1-6}haloalkyl, -O-haloC_{1-6}alkyl, -SO_2R^c, - NR^cR^d, -CN, -C(=O)NR^cR^d, - C(=O)R^c, -OC(=O)R^a, -C(=O)OR^c, -$B(OH)_2$, a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl, and heterocycloalkyl groups have 1, 2, 3, or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group , and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2;

wherein each R^a, R^b, R^c, and R^d is independently H, OH, -C_{1-6}alkyl, -C_{1-6}alkenyl, -C_{2-6}alkynyl, -C_{1-6}alkyl-$NR^{14}R^{14}$, $NR^{14}R^{14}$, -SO_2R^{14}, -$(CH_2CH_2O)_nCH_3$, (=O), -C(=O)R^{14}, -OC(=O)R^{14}, -C(=O)OR^{14}, -C(=O)$NR^{14}R^{14}$, C_{1-6}haloalkyl, -O-haloC_{1-6}alkyl, -C_{1-6}alkyl-O-C_{1-6}alkyl, -C_{1-6}alkyl-OH, benzyl, phenyl, a -C_{1-6}alkyl–3- to 12-membered heterocycloalkyl, a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl, and heterocycloalkyl groups andr the heterocycloalkyl group of the -C_{1-6}alkyl–heterocycloalkyl group have 1, 2, 3, or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, heterocycloalkyl, and the heterocycloalkyl groups of the -C_{1-6}alkyl–heterocycloalkyl group may include a C=O group, and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2;

the alkyl, aryl, heteroaryl, spirocycloalkyl, spiroheterocycloalkyl, cycloalkyl, heterocycloalkyl and the heterocycloalkyl groups of the -C_{1-6}alkyl–heterocycloalkyl groups of R^a, R^b, R^c, and R^d can be unsubstituted or substituted with 1, 2, 3, or 4 R^{14} substituents independently selected from H, OH, -N=N=N, halo, -C_{1-6}alkyl, -OC_{1-6}alkyl, C_{1-6}haloalkyl, -O-haloC_{1-6}alkyl, phenyl, tolyl, -C(O)C_{1-6}alkyl, -C(O)OCH_3, SO_2-phenyl, or -SO_2-N$(CH_3)_2$; and

n is independently, in each instance, an integer of 1, 2, 3 or 4.

2. Another embodiment of the present invention comprises the compound of Embodiment 1, wherein the compound of Formula I' has the Formula I'a:



(I'a)

or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof.

3. The compound of any one of Embodiments 1 or 2, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein b is a double bond.

4. The compound of any one of Embodiments 1 or 2, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the

pharmaceutically acceptable salt of the stereoisomer thereof, wherein b is a single bond.

5. The compound of any one of Embodiments 1-4, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein Z is C.

6. The compound of any one of Embodiments 1-4, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein Z is N.

7. The compound of any one of Embodiments 1-6, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein Q is O.

8. The compound of any one of Embodiments 1-6, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein Q is S.

9. The compound of any one of Embodiments 1-8, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein W is C=O.

10. The compound of any one of Embodiments 1-8, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein W is $CR^{WA}R^{WB}$.

11. The compound of any one of Embodiments 1-8 and 10, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{WA} and R^{WB} are both H.

12. The compound of any one of Embodiments 1-11, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^1 is halo.

13. The compound of any one of Embodiments 1-12, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^1 is Cl.

14. The compound of any one of Embodiments 1-13, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^2 is H.

15. The compound of any one of Embodiments 1-14, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^3 is H or -C_{1-6} alkyl.

16. The compound of any one of Embodiments 1-15, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^3 is -CH_3.

17. The compound of any one of Embodiments 1-15, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^3 is H.

18. The compound of any one of Embodiments 1-17, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^4 is independently selected from H, -C_{1-6}alkyl, -C_{1-6}alkylhalo, -C_{1-6}alkyl-O-C_{1-6}alkyl, or -$(CH_2CH_2O)_nR^a$, wherein the -C_{1-6}alkyl is unsubstituted or substituted with –OH, (=O), phenyl, -O-$SiR^aR^bR^c$, -NR^aR^b, a 3- to 12-membered cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl having 1, 2, 3, or 4 heteroatoms independently selected from O, N or S.

19. The compound of any one of Embodiments 1-18, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^4 is H.

20. The compound of any one of Embodiments 1-18, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the

pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^4 is -C_{1-6}alkyl.

21 The compound of any one of Embodiments 1-18 or 20, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^4 is -CH_3.

22. The compound of any one of Embodiments 1-18, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^4 is -C_{1-6}alkyl-O-C_{1-6}alkyl.

23. The compound of any one of Embodiments 1-18 or 22, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^4 is -$CH_2CH_2OCH_3$.

24. The compound of any one of Embodiments 1-18, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^4 is -C_{1-6}alkyl-OH.

25. The compound of any one of Embodiments 1-18, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^4 is -C_{1-6}alkyl=O.

26. The compound of any one of Embodiments 1-18, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^4 is -C_{1-6}alkyl-phenyl.

27. The compound of any one of Embodiments 1-18, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^4 is -C_{1-6}alkyl-O-$SiR^aR^bR^c$.

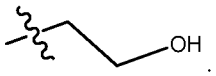
28. The compound of any one of Embodiments 1-18, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the

pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^4 is -C_{1-6}alkyl-NR^aR^b.

29. The compound of any one of Embodiments 1-18, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^4 is -C_{1-6}alkyl-C_3-C_6cycloalkyl.

30. The compound of any one of Embodiments 1-18, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^4 is -C_{1-6}alkyl-C_3-C_{10}heterocycloalkyl having 1, 2, 3, or 4 heteroatoms independently selected from O, N or S.

31. The compound of any one of Embodiments 1-18, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^4 is



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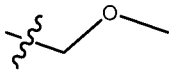
32. The compound of any one of Embodiments 1-18, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^4 is



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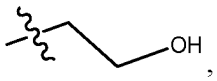
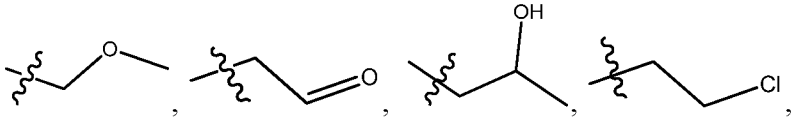
33. The compound of any one of Embodiments 1-18, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^4 is independently selected from $-CH_3$, $-CH_2CH_2OCH_3$,  ,



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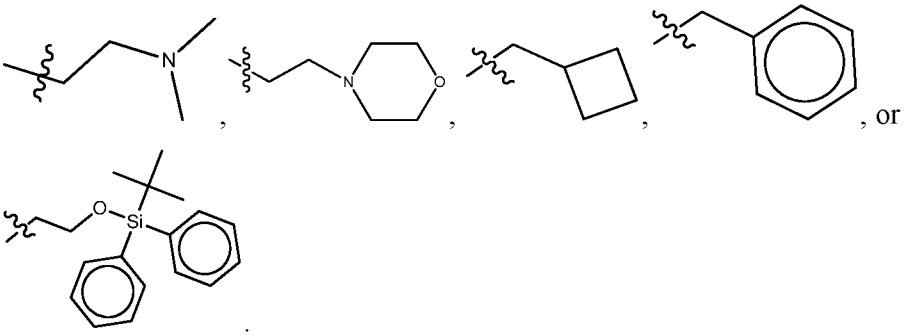
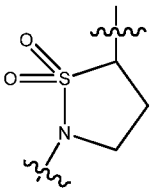


34. The compound of any one of Embodiments 1-14, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^3 and R^4, together with the atoms to which they are bonded, form a 5- to 12-membered ring, optionally containing a heteroatom selected from N, O or S in addition to the S and N atoms present in the ring, wherein the ring may optionally contain at least one double bond; and further wherein the ring is substituted with 0, 1, 2, or 3 R^{3A} substituents.

35. The compound of any one of Embodiments 1-14 or 34, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^3 and R^4 together with the atoms to which they are attached form



36. The compound of any one of Embodiments 1-35, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^5 is H or -C_{1-6} alkyl.

37. The compound of any one of Embodiments 1-36, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^5 is -CH_3.

38. The compound of any one of Embodiments 1-36, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^5 is H.

39. The compound of any one of Embodiments 1-38, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^6 is H or -C_{1-6} alkyl.

40. The compound of any one of Embodiments 1-38, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^6 is -CH_3.

41. The compound of any one of Embodiments 1-38, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^6 is H.

42. The compound of any one of Embodiments 1-41, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein each of R^{4A}, R^{5A}, R^{6A}, R^{7A} and R^{8A} is independently selected from H, OH, halo, or -C_{1-6}alkyl.

43 The compound of Embodiment 42, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein each of R^{4A}, R^{5A}, R^{6A}, R^{7A} and R^{8A} is H.

44. The compound of any one of Embodiments 1, 2, or 4-43, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{7A} and R^{8A} are both H.

45. The compound of any one of Embodiments 1-44, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^7 and R^8 are both H.

46. The compound of any one of Embodiments 1-45, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^9 is independently selected from H, -C_{1-6}alkyl, -C_{2-6}alkenyl, or -C_{1-6}alkyl-O-C_{1-6}alkyl or -C_{1-6}haloalkyl.

47. The compound of any one of Embodiments 1-46, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^9 is H.

48. The compound of any one of Embodiments 1-46, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^9 is $-CH_3$.

49. The compound of any one of Embodiments 1-46, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^9 is $-CH_2CH_3$.

50. The compound of any one of Embodiments 1-46, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^9 is $-CH_2CH(CH_3)_2$.

51. The compound of any one of Embodiments 1-46, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^9 is $-CH_2CH_2OCH_3$.

52. The compound of any one of Embodiments 1-46, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^9 is $-CF_3$.

53. The compound of any one of Embodiments 1-52, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is selected from H, C_{1-6}haloalkyl, C_{1-6}alkyl, $-C_{2-6}$alkenyl $-(CH_2CH_2O)_nR^a$, $-SO_2R^a$, $-C(=O)R^a$,$-C(=O)OR^a$, $-C(=O)NR^aR^b$, $-NR^aR^b$, $-N=N=N$, $-C_{1-6}$alkyl-O-C_{1-6}alkyl, a 6- to 12-membered aryl, a 6- to 12-membered heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl and heterocycloalkyl groups have 1, 2, 3, or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group, and

further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2.

54. The compound of any one of Embodiments 1-53, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is -C_{1-6}alkyl.

55. The compound of any one of Embodiments 1-53, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is -C(=O)R^a.

56. The compound of any one of Embodiments 1-53, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heterocycloalkyl group has 1, 2, 3 or 4 heteroatoms independently selected from O, N or S.

57. The compound of any one of Embodiments 1-53, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is a 3- to 12-membered monocyclic heterocycloalkyl group, wherein the heterocycloalkyl group has 1, 2, 3 or 4 heteroatoms independently selected from O or N.

58. The compound of any one of Embodiments 1-53, 56 or 57, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein the 3- to 12-membered monocyclic heterocycloalkyl R^{9A} group can be unsubstituted or substituted with 1, 2, 3 or 4 R^{10} substituents independently selected from OH, halo, -NR^cR^d, -C_{1-6}alkyl, -C_2-C_6 alkenyl, -C_2-C_6alkynyl, -OC_{1-6}alkyl, -C_{1-6}alkyl-OH, -C_{1-6}alkyl-O-C_{1-6}alkyl, C_{1-6}haloalkyl, -O-haloC_{1-6}alkyl, -SO_2R^c, -CN, -C(=O)NR^cR^d, -C(=O)R^c, -OC(=O)R^a, -C(=O)OR^c , a 6- to 12-membered aryl, a 6- to 12-membered heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl, or

heterocycloalkyl group have from 1, 2, 3, or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group, and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2.

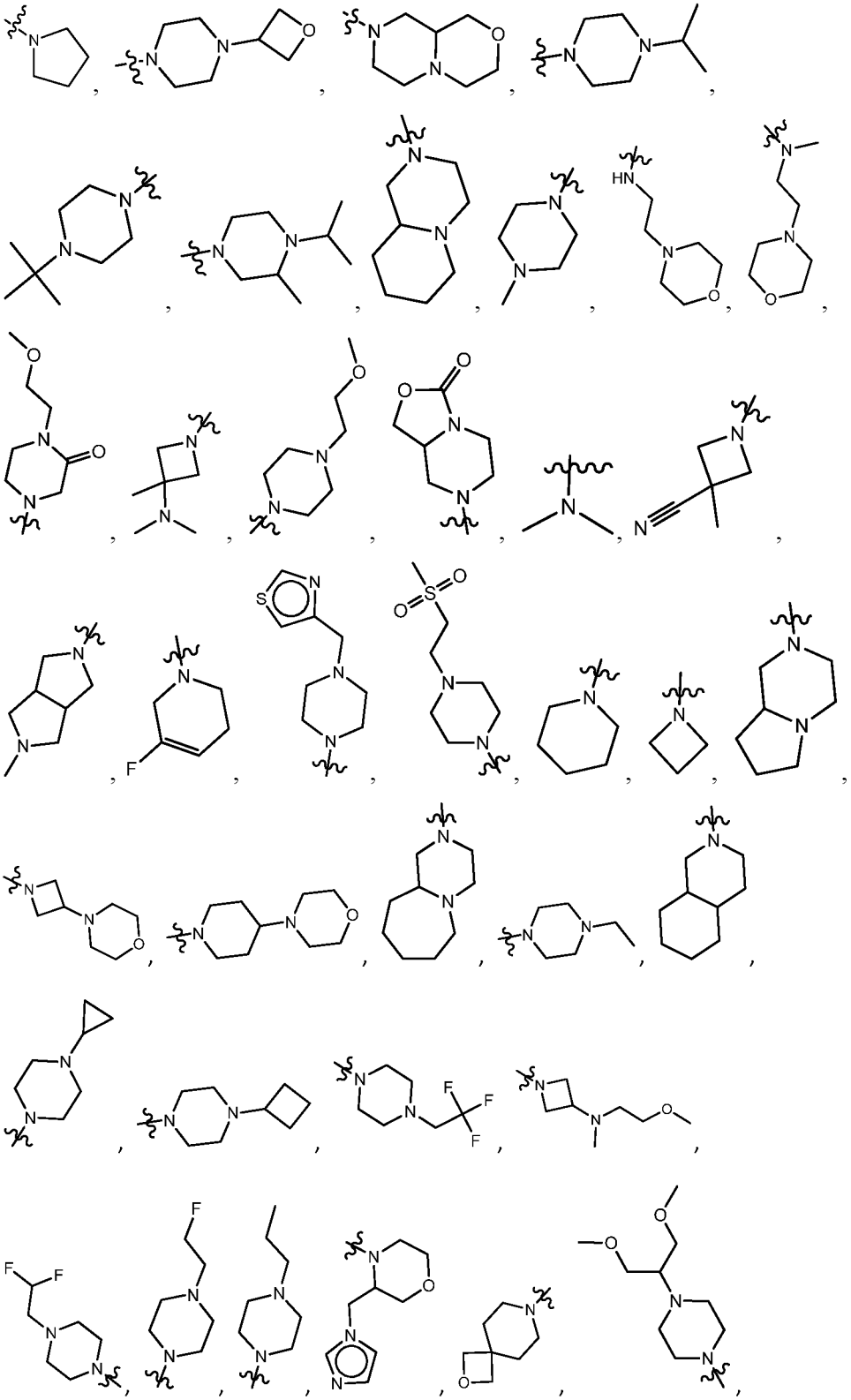
59. The compound of any one of Embodiments 1-58, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein the 1, 2, 3 or 4 R^{10} substituents are independently selected from -C_{1-6}alkyl or a 3- to 12-membered monocyclic heterocycloalkyl group, wherein the heterocycloalkyl group has 1, 2, 3 or 4 heteroatoms independently selected from O, N or S.

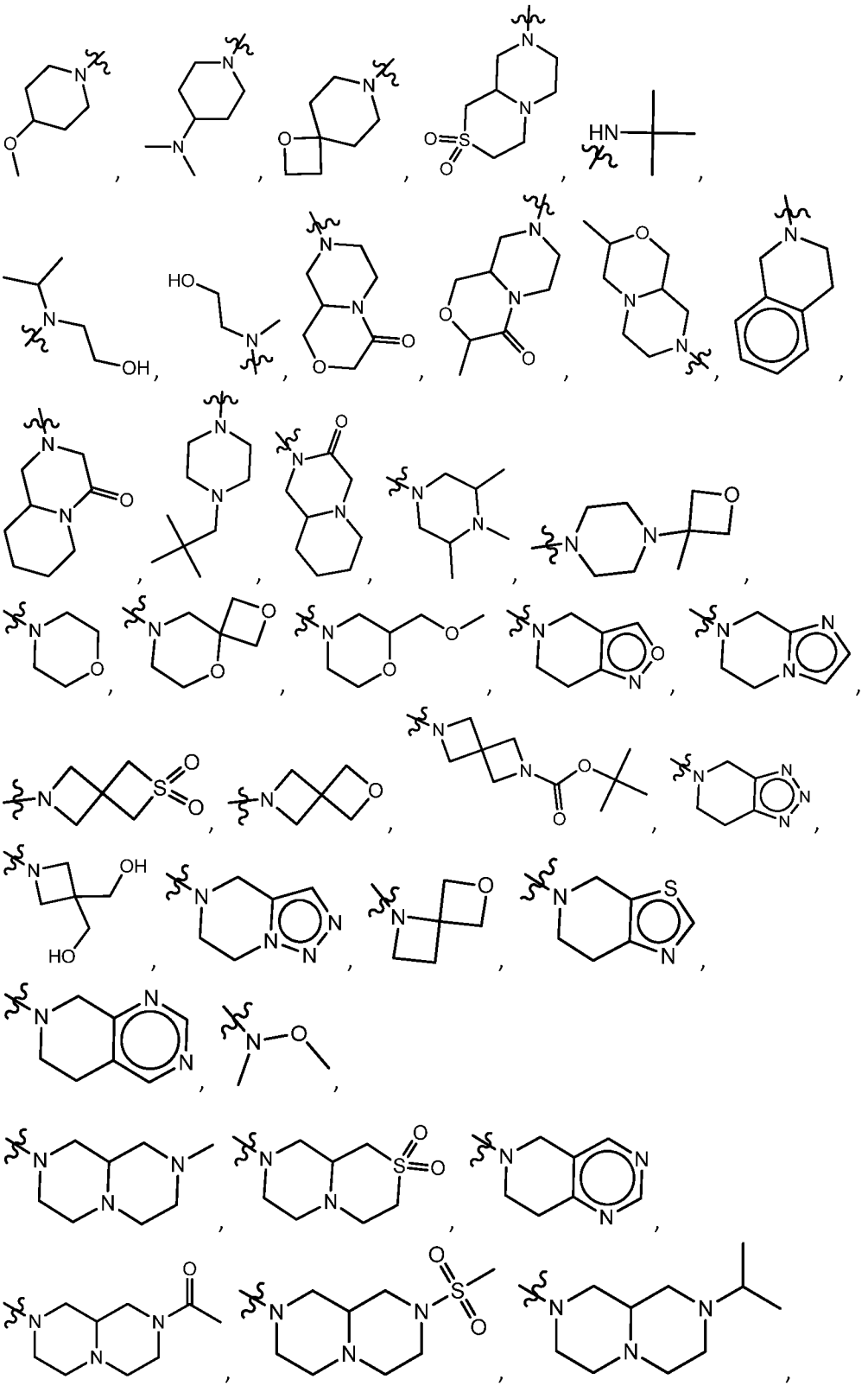
60. The compound of of any one of Embodiments 1-59, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{10} is -C_{1-6}alkyl.

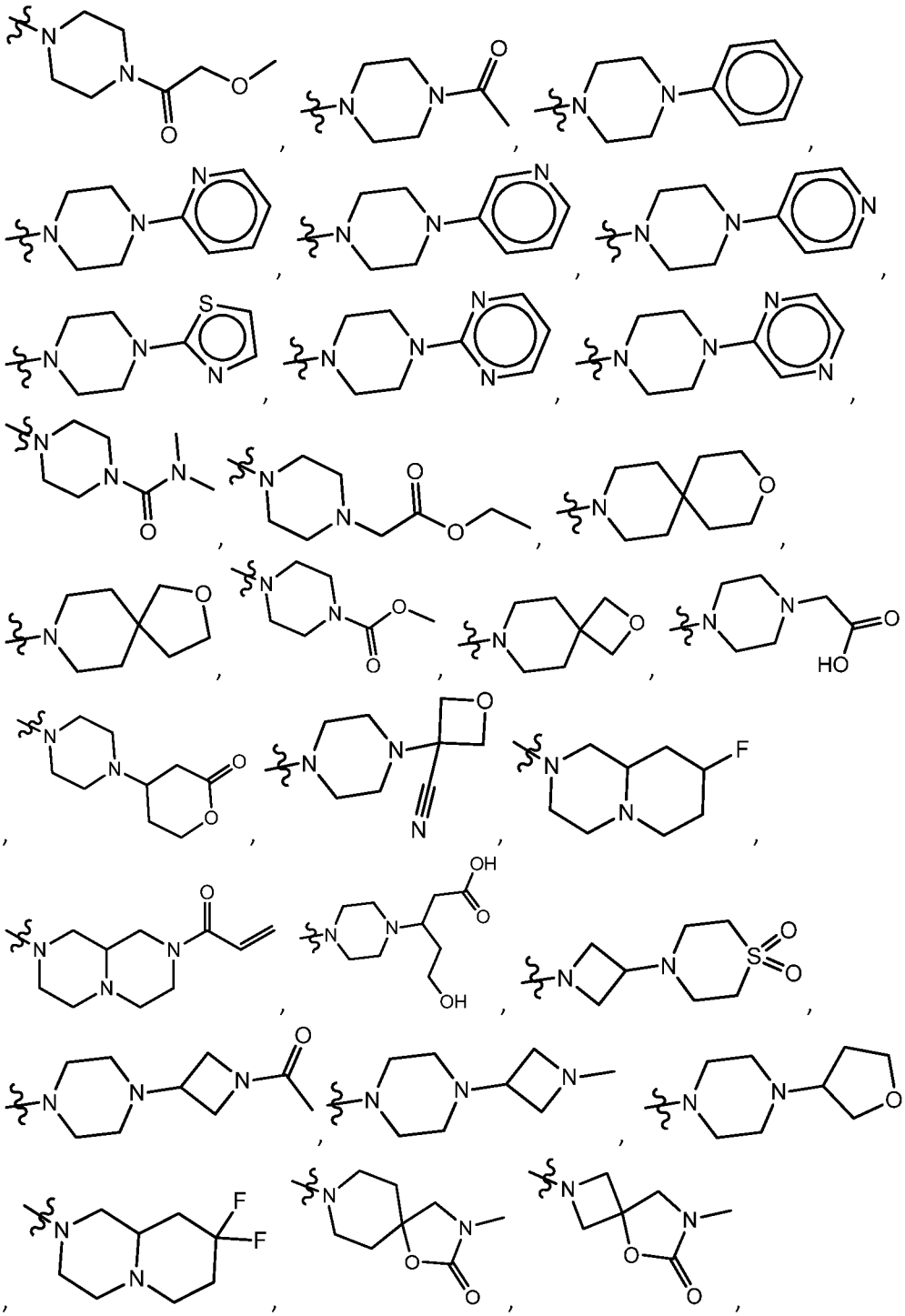
61. The compound of any one of Embodiments 1-59, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{10} is a 3- to 12-membered monocyclic heterocycloalkyl group, wherein the heterocycloalkyl group has 1, 2, 3 or 4 heteroatoms independently selected from O, N or S.

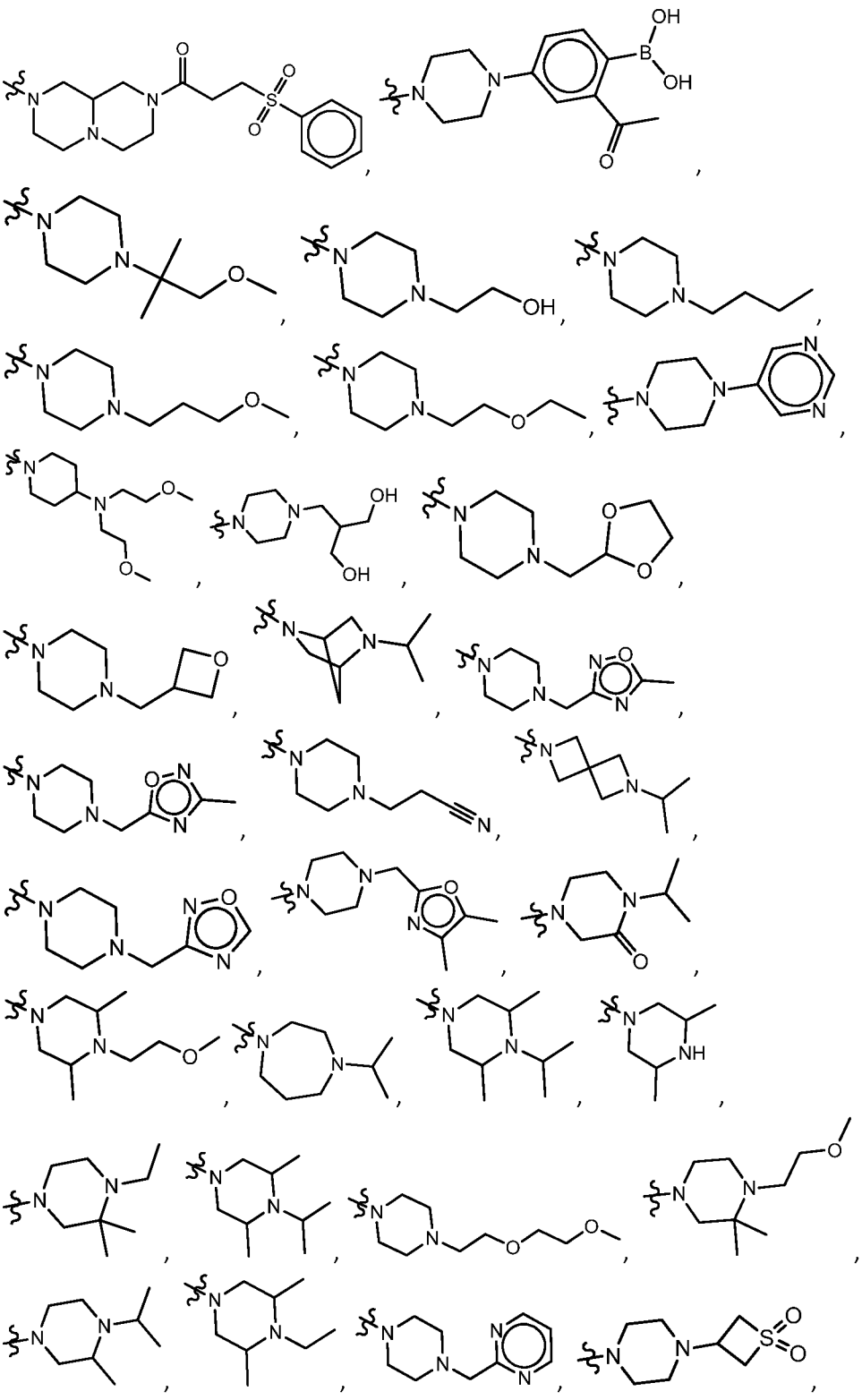
62. The compound of any one of Embodiments 1-53, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is a 5- to 12-membered bicyclic heterocycloalkyl group, wherein the heterocycloalkyl group has 1, 2, 3 or 4 heteroatoms independently selected from O or N.

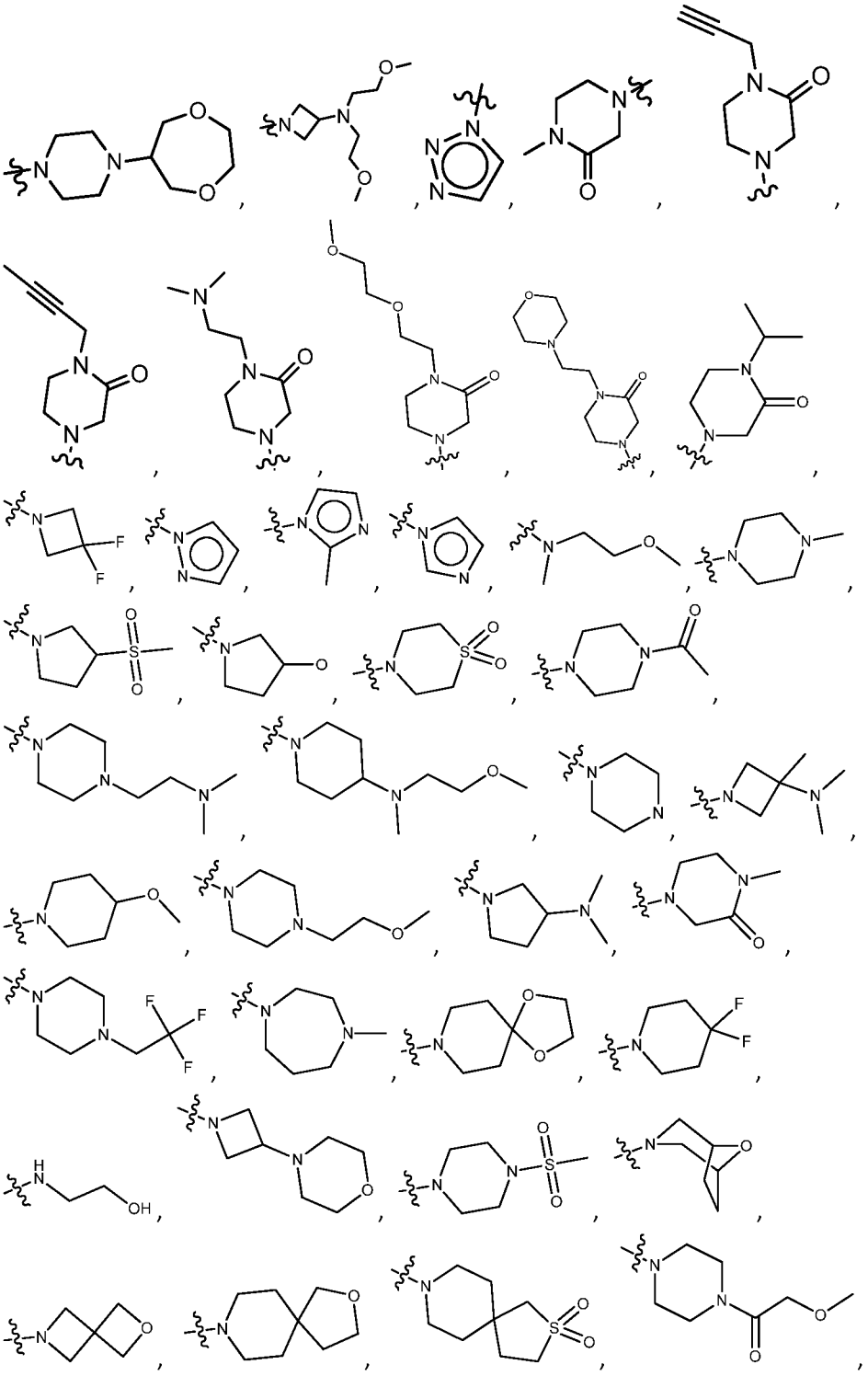
63. The compound of any one of Embodiments 1-52, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is independently selected from -N=N=N,

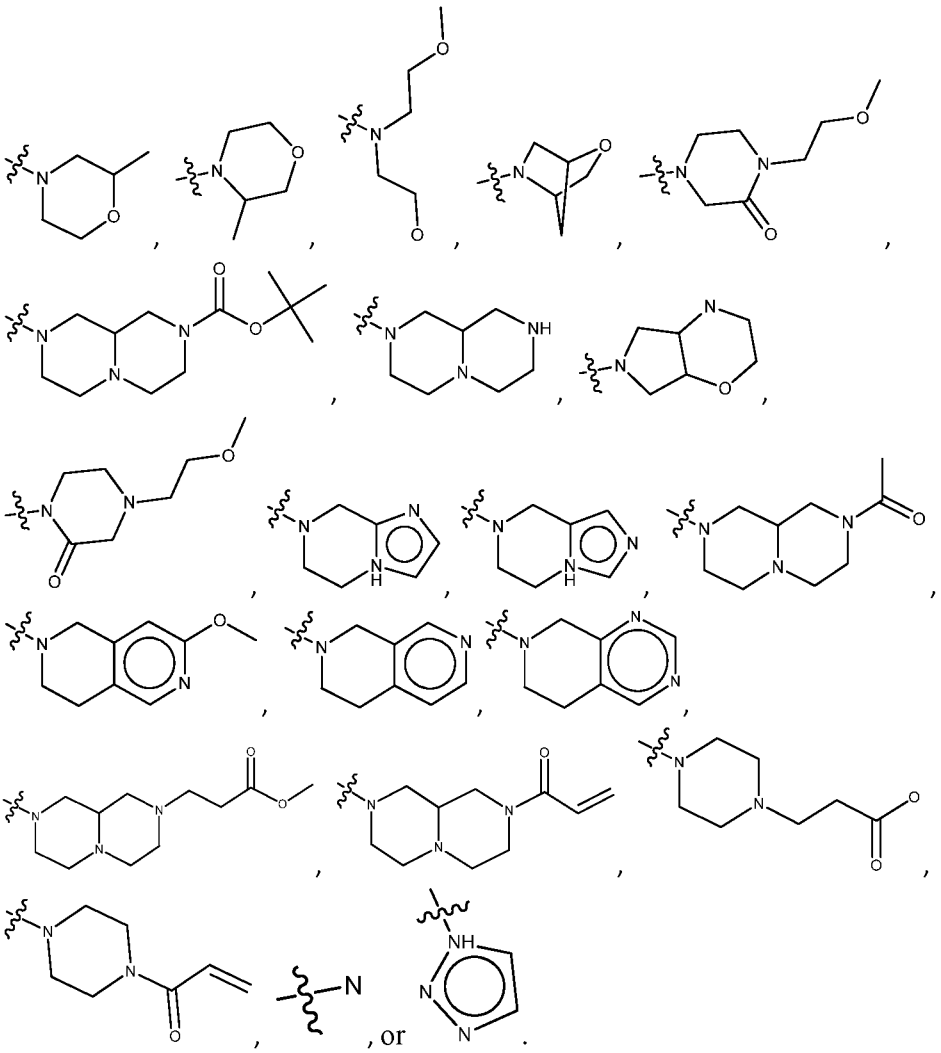








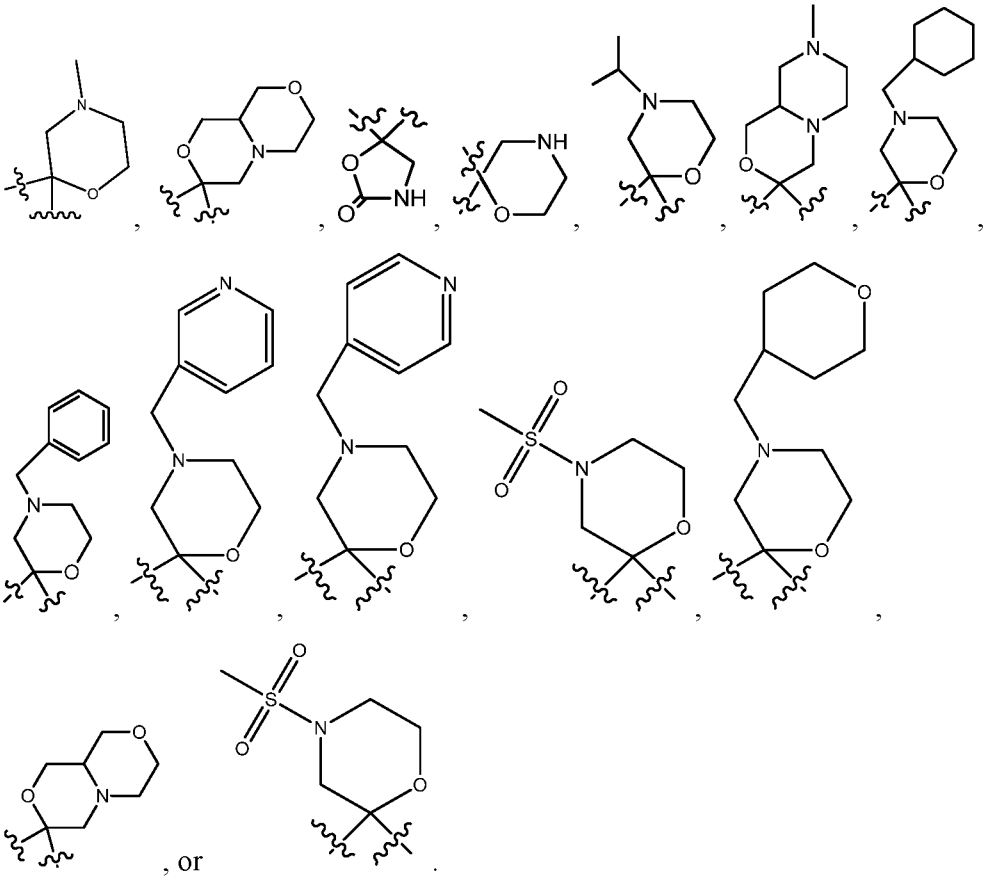




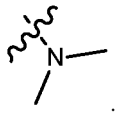
64. The compound of any one of Embodiments 1-45, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^9 and R^{9A} together with Q, W, and the C to which W and Q are bonded, form a 3- to 12-membered monocyclic or bicyclic ring, optionally containing a heteroatom in addition to Q selected from N, O or S, wherein the ring may contain a double bond, wherein the ring may optionally include a C=O group, and further wherein the ring optionally may be substituted by 1, 2, or 3 R^{11} substituents.

65. The compound of any one of Embodiments 1-45 and 64, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the

pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^9 and R^{9A} together with the atoms to which they are bonded form a structure selected from:

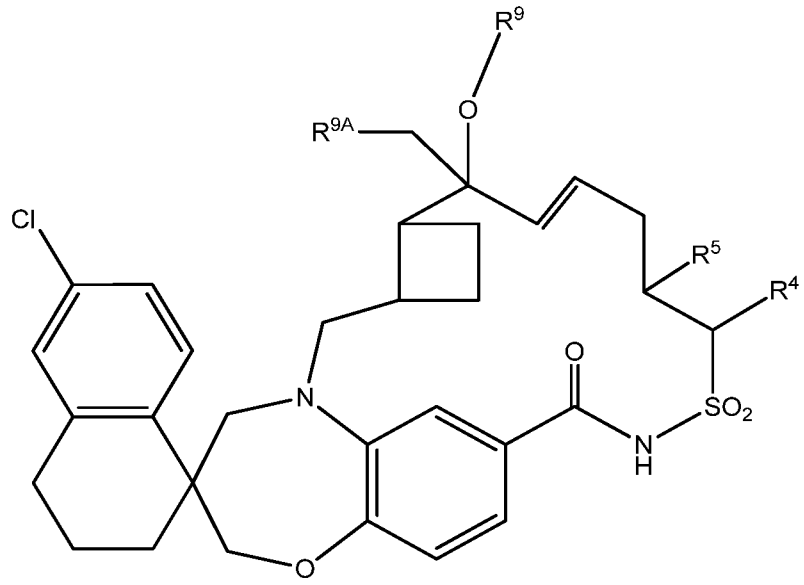


, or .

66. The compound of any one of Embodiments 1-9, 12-52 or 64, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein when W is C=O, then R^{9A} is  .

67. The compound of any one of Embodiments 1-11 or 14-66, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^1 is H.

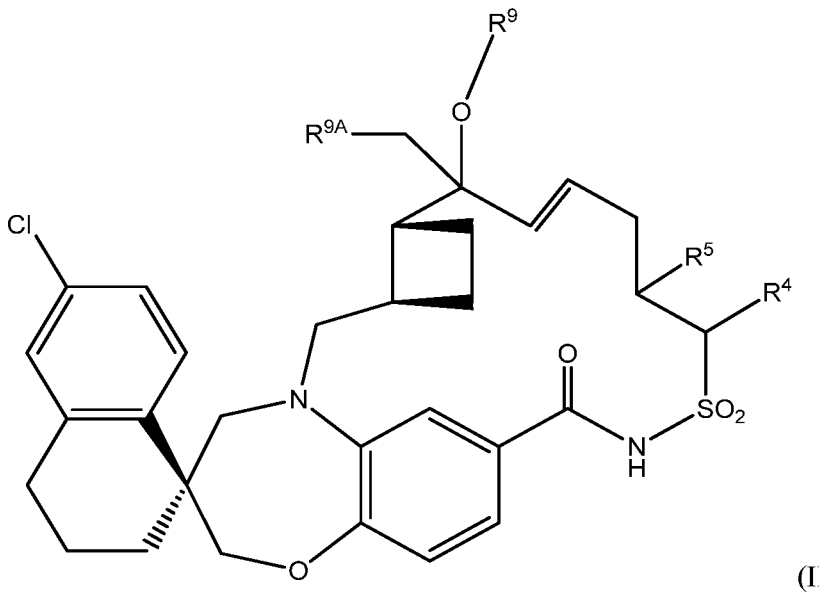
68. Another embodiment of the present invention comprises the compound of Embodiment 1, wherein the compound of Formula I' has Formula II':



(II')

or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof.

69. Another embodiment of the present invention comprises the compound of any one of Embodiments 1, 2, or 68, wherein the compound of Formula I' has Formula II'a:



(II'a)

or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof.

70. The compound of any one of Embodiments 1, 2, 68, or 69, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^4 is independently selected from H, -C_{1-6}alkyl, -C_{1-6}alkylhalo, -C_{1-6}alkyl-O-C_{1-6}alkyl, or -$(CH_2CH_2O)_nR^a$, wherein the -C_{1-6}alkyl is unsubstituted or substituted with –OH, (=O), phenyl, -O-$SiR^aR^bR^c$, -NR^aR^b, a 3- to 12-membered cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl having 1, 2, 3, or 4 heteroatoms independently selected from O, N or S.

71. The compound of any one of Embodiments 1, 2, 68-69, or 70, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^4 is $–CH_3$.

72. The compound of any one of Embodiments 1, 2, 68-69, or 70, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^4 is $–CH_2CH_2OCH_3$.

73. The compound of any one of Embodiments 1, 2, 68-71 or 72, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^5 is H or -C_{1-6} alkyl.

74. The compound of any one of Embodiments 1, 2, 68-71 or 72, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^5 is -CH_3.

75. The compound of any one of Embodiments 1, 2, 68-71 or 72, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^5 is H.

76. The compound of any one of Embodiments 1, 2, 68-74 or 75, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^6 is H or -C_{1-6} alkyl.

77. The compound of any one of Embodiments 1, 2, 68-75 or 76, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^6 is -CH_3.

78. The compound of any one of Embodiments 1, 2, 68-75 or 76, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^6 is H.

79. The compound of any one of Embodiments 1, 2, 68-77 or 78 or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^9 is independently selected from H, -C_{1-6}haloalkyl, -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -$(CH_2CH_2O)_nR^a$, -$C(=O)R^a$, -$C(=O)OR^a$, -$C(=O)NR^aR^b$, -C_{1-6}alkyl-O-C_{1-6}alkyl, a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl,

spiroheterocycloalkyl and heterocycloalkyl groups have 1, 2, 3, or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group, and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2.

80. The compound of any one of Embodiments 1, 2, 68-78 or 79, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^9 is $-CH_3$.

81. The compound of any one of Embodiments 1, 2, 68-78 or 79, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^9 is $-CH_2CH_3$.

82. The compound of any one of Embodiments 1, 2, 68-80 or 81, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is independently selected from H, C_{1-6}haloalkyl, C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl -$(CH_2CH_2O)_nR^a$, -SO_2R^a, -$C(=O)R^a$,-$C(=O)OR^a$, -$C(=O)NR^aR^b$, -NR^aR^b, -N=N=N, -C_{1-6}alkyl-O-C_{1-6}alkyl, a 6- to 12-membered aryl, a 6- to 12-membered heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl and heterocycloalkyl groups have 1, 2, 3, or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group, and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2.

83. The compound of any one of Embodiments 1, 2, 68-81 or 82, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the

pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is -C_{1-6}alkyl.

84. The compound of any one of Embodiments 1, 2, 68-81 or 82, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is -C(=O)R^a.

85. The compound of any one of Embodiments 1, 2, 68-81 or 82, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heterocycloalkyl group has 1, 2, 3 or 4 heteroatoms independently selected from O, N or S.

86. The compound of any one of Embodiments 1, 2, 68-82 or 85, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is a 3- to 12-membered monocyclic heterocycloalkyl group, wherein the heterocycloalkyl group has 1, 2, 3 or 4 heteroatoms independently selected from O or N.

87. The compound of any one of Embodiments 1, 2, 68-82 or 85-86, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein the 3- to 12-membered monocyclic heterocycloalkyl R^{9A} group can be unsubstituted or substituted with 1, 2, 3 or 4 R^{10} substituents independently selected from OH, halo, -NR^cR^d, -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -OC_{1-6}alkyl, -C_{1-6}alkyl-OH, -C_{1-6}alkyl-O-C_{1-6}alkyl, C_{1-6}haloalkyl, -O-haloC_{1-6}alkyl, -SO_2R^c, -CN, -C(=O)NR^cR^d, -C(=O)R^c, -OC(=O)R^a, -C(=O)OR^c, a 6- to 12-membered aryl, a 6- to 12-membered heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl, and

heterocycloalkyl groups have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group, and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2.

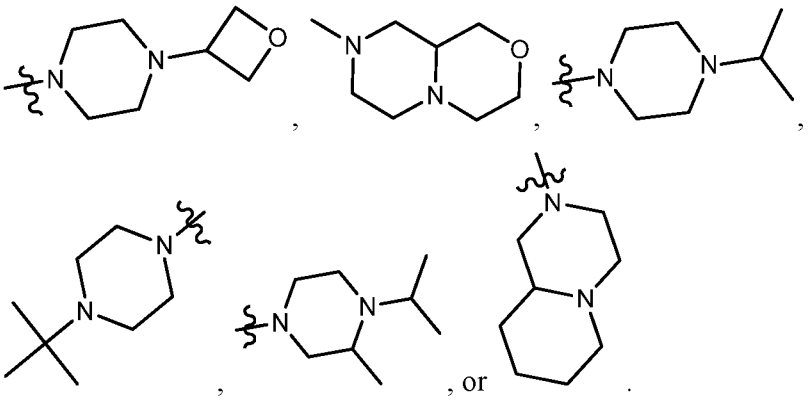
88. The compound of any one of Embodiments 1, 2, 68-82 or 85-86, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein the 1, 2, 3 or 4 R^{10} substituents are independently selected from -C_{1-6}alkyl or a 3- to 12-membered monocyclic heterocycloalkyl group, wherein the heterocycloalkyl group has 1, 2, 3 or 4 heteroatoms independently selected from O, N or S.

89. The compound of any one of Embodiments 1, 2, 68-82 or 85-88, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{10} is -C_{1-6}alkyl.

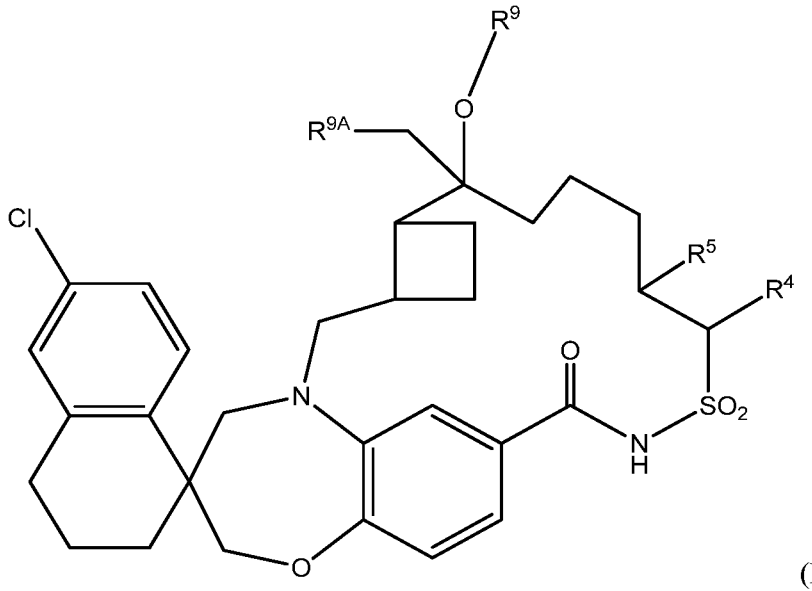
90. The compound of any one of Embodiments 1, 2, 68-82 or 85-88, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{10} is a 3- to 12-membered monocyclic heterocycloalkyl group, wherein the heterocycloalkyl group has 1, 2, 3 or 4 heteroatoms independently selected from O, N or S.

91. The compound of any one of Embodiments 1, 2, 68-82 or 85, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is a 5- to 12-membered bicyclic heterocycloalkyl group, wherein the heterocycloalkyl group has 1, 2, 3 or 4 heteroatoms independently selected from O or N.

92. The compound of any one of Embodiments 1, 2, or 68-82, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is independently selected from:



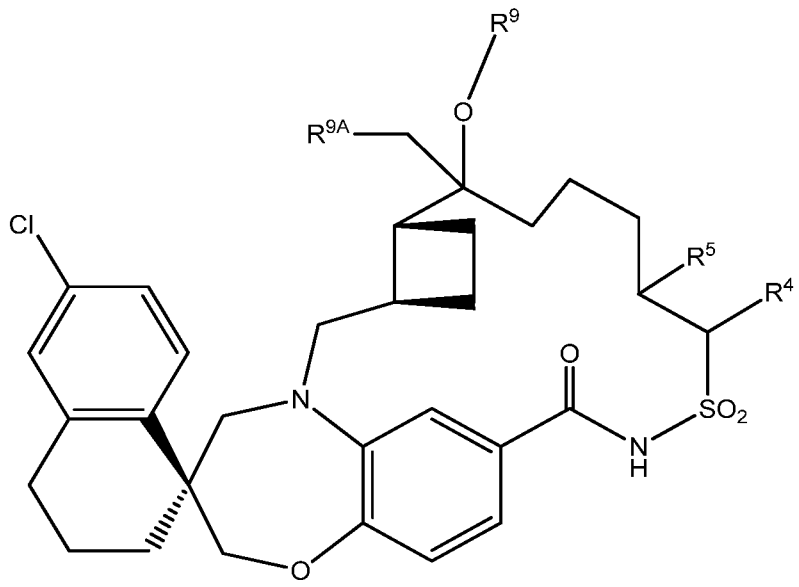
93. Another embodiment of the present invention comprises the compound of Embodiment 1, wherein the compound of Formula I' has Formula III':



(III')

or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^4, R^5, R^9 and R^{9A} are as defined above.

94. Another embodiment of the present invention comprises the compound of Embodiment 1, 2, or 93, wherein the compound of Formula I' has Formula III'a:



(III'a)

or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof.

95. The compound of any one of Embodiments 1, 2, or 93-94, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^4 is independently selected from H, -C_{1-6}alkyl, -C_{1-6}alkylhalo, -C_{1-6}alkyl-O-C_{1-6}alkyl, or -$(CH_2CH_2O)_nR^a$, wherein the -C_{1-6}alkyl is unsubstituted or substituted with –OH, -(=O), phenyl, -O-$SiR^aR^bR^c$, -NR^aR^b, a 3- to 12-membered cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl having 1, 2, 3, or 4 heteroatoms independently selected from O, N or S.

96. The compound of any one of Embodiments 1, 2, or 93-95, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^4 is $–CH_3$.

97. The compound of any one of Embodiments 1, 2, or 93-95, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^4 is $–CH_2CH_2OCH_3$.

98. The compound of any one of Embodiments 1, 2 or 93-97, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^5 is H or -C_{1-6}alkyl.

99. The compound of any one of Embodiments 1, 2 or 93-98, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^5 is -CH_3.

100. The compound of any one of Embodiments 1, 2 or 93-98, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^5 is H.

101. The compound of any one of Embodiments 1, 2 or 93-100, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^6 is H or -C_{1-6}alkyl.

102. The compound of any one of Embodiments 1, 2 or 93-101, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^6 is -CH_3.

103. The compound of any one of Embodiments 1, 2 or 93-101, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^6 is H.

104. The compound of any one of Embodiments 1, 2 or 93-103, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^9 is independently selected from H, -C_{1-6}haloalkyl, -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -$(CH_2CH_2O)_nR^a$, -$C(=O)R^a$, -$C(=O)OR^a$, -$C(=O)NR^aR^b$, -C_{1-6}alkyl-O-C_{1-6}alkyl, a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl,

spiroheterocycloalkyl and heterocycloalkyl groups have 1, 2, 3, or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group, and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2.

105. A compound of any one of Embodiments 1, 2 or 93-104, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^9 is $–CH_3$.

106. A compound of any one of Embodiments 1, 2 or 93-104, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^9 is $–CH_2CH_3$.

107. A compound of any one of Embodiments 1, 2 or 93-104, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^9 is –H.

108. A compound of any one of Embodiments 1, 2 or 93-107, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is independently selected from H, C_{1-6}haloalkyl, C_{1-6}alkyl, -C_{2-6}alkenyl -$(CH_2CH_2O)_nR^a$, $-SO_2R^a$, $-C(=O)R^a$,$-C(=O)OR^a$, $-C(=O)NR^aR^b$, $-NR^aR^b$, -N=N=N, -C_{1-6}alkyl-O-C_{1-6}alkyl, a 6- to 12-membered aryl, a 6- to 12-membered heteroaryl, a 5- to 10-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl and heterocycloalkyl groups have 1, 2, 3, or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group, and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2.

109. The compound of any one of Embodiments 1, 2 or 93-108, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is -C_{1-6}alkyl.

110. The compound of any one of Embodiments 1, 2 or 93-108, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is -C(=O)R^a.

111. The compound of any one of Embodiments 1, 2 or 93-108, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heterocycloalkyl group has 1, 2, 3 or 4 heteroatoms independently selected from O, N or S.

112. The compound of any one of Embodiments 1, 2, 93-108 or 111, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is a 3- to 12-membered monocyclic heterocycloalkyl group, wherein the heterocycloalkyl group has 1, 2, 3 or 4 heteroatoms independently selected from O or N.

113. The compound of any one of Embodiments 1, 2, 93-108 or 112, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein the 3- to 12-membered monocyclic heterocycloalkyl R^{9A} group can be unsubstituted or substituted with from 1, 2, 3 or 4 R^{10} substituents independently selected from OH, halo, -NR^cR^d, -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -OC_{1-6}alkyl, -C_{1-6}alkyl-OH, -C_{1-6}alkyl-O-C_{1-6}alkyl, C_{1-6}haloalkyl, -O-haloC_{1-6}alkyl, -SO_2R^c, -CN, -C(=O)NR^cR^d, -C(=O)R^c, -OC(=O)R^a, -C(=O)OR^c , a 6- to 12-membered aryl, a 6- to 12-membered heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered

monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl, and heterocycloalkyl groups have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group , and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2.

114. The compound of any one of Embodiments 1, 2, 93-108 or 112-113, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein the 1, 2, 3 or 4 R^{10} substituents are independently selected from -C_{1-6}alkyl or a 3- to 12-membered monocyclic heterocycloalkyl group, wherein the heterocycloalkyl group has 1, 2, 3 or 4 heteroatoms independently selected from O, N or S.

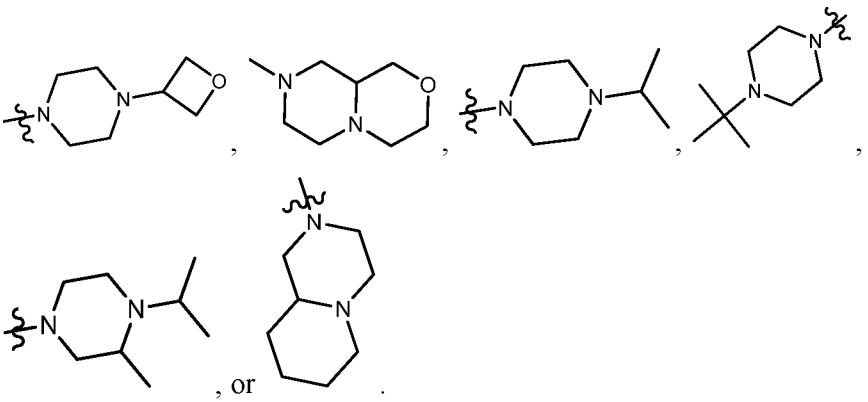
115. The compound of any one of Embodiments 1, 2, 93-108 and 112-114, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{10} is -C_{1-6}alkyl.

116. The compound of any one of Embodiments 1, 2, 93-108 or 112-113, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{10} is a 3- to 12-membered monocyclic heterocycloalkyl group, wherein the heterocycloalkyl group has from 1, 2, 3 or 4 heteroatoms independently selected from O, N or S.

117. The compound of any one of Embodiments 1, 2, 93-108 or 111, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is a 5- to 12-membered bicyclic heterocycloalkyl group, wherein the heterocycloalkyl group has 1, 2, 3 or 4 heteroatoms independently selected from O or N.

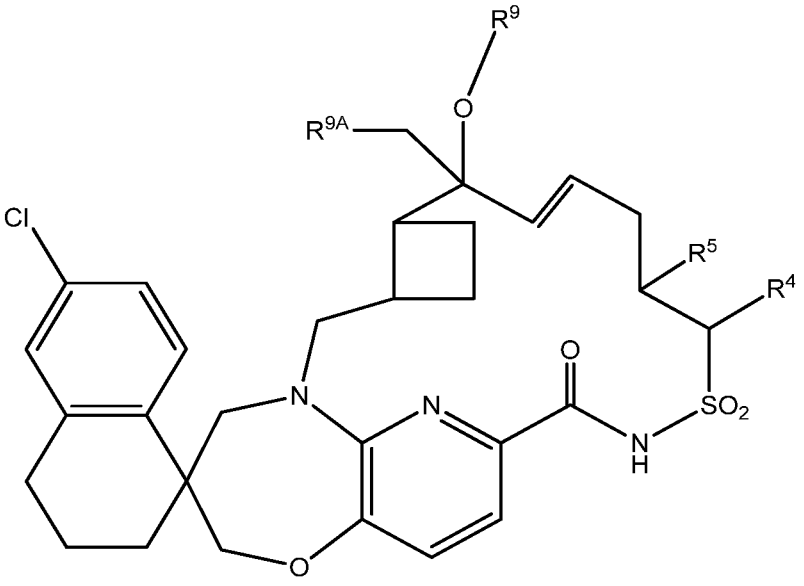
118. The compound of any one of Embodiments 1, 2, or 93-108, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the

pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is independently selected from:



, or .

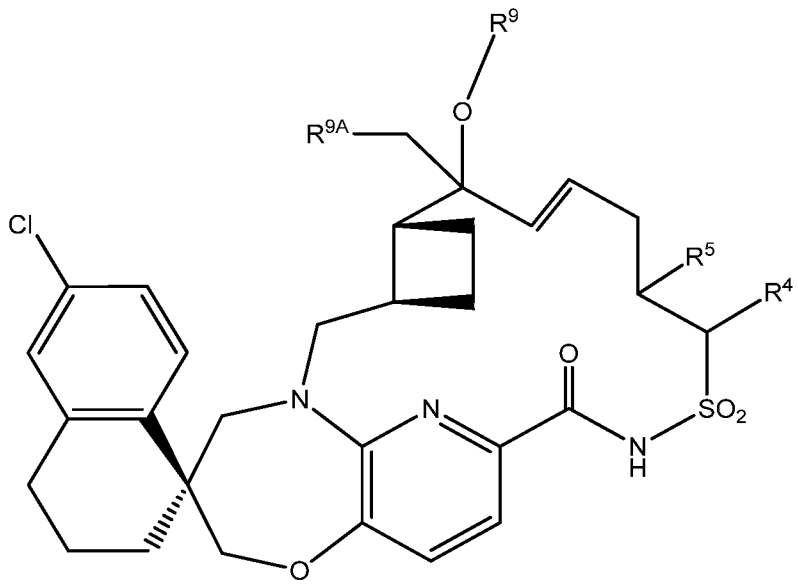
119. Another embodiment of the present invention comprises the compound of Embodiment 1, wherein the compound of Formula I' has Formula IV':



(IV')

or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^4, R^5, R^9 and R^{9A} are as defined above.

120. Another embodiment of the present invention comprises the compound of Embodiment 1, 2 or 119, wherein the compound of Formula I' has Formula IV'a:



(IV'a)

or a stereoisomer thereof, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of the stereoisomer thereof.

121. The compound of any one of Embodiments 1, 2, or 119-120, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^4 is independently selected from H, -C_{1-6}alkyl, -C_{1-6}alkylhalo, -C_{1-6}alkyl-O-C_{1-6}alkyl, or -$(CH_2CH_2O)_nR^a$, wherein the -C_{1-6}alkyl is unsubstituted or substituted with –OH, -(=O), phenyl, -O-$SiR^aR^bR^c$, -NR^aR^b, a 3- to 12-membered cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl having 1, 2, 3, or 4 heteroatoms independently selected from O, N or S.

122. The compound of any one of Embodiments 1, 2, or 119-121, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^4 is $–CH_3$.

123. The compound of any one of Embodiments 1, 2, or 119-121, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the

pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^4 is $-CH_2CH_2OCH_3$.

124. The compound of any one of Embodiments 1, 2, or 119-123, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^5 is H or -C_{1-6} alkyl.

125. The compound of any one of Embodiments 1, 2, or 119-124, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^5 is $-CH_3$.

126. The compound of any one of Embodiments 1, 2, or 119-125, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^5 is H.

127. The compound of any one of Embodiments 1, 2, or 119-126, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^6 is H or -C_{1-6} alkyl.

128. The compound of any one of Embodiments 1, 2, or 119-127, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^6 is $-CH_3$.

129. The compound of any one of Embodiments 1, 2, or 119-127, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^6 is H.

130. The compound of any one of Embodiments 1, 2, or 119-129, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^9 is independently selected from H, -C_{1-6}haloalkyl, -C_{1-6}alkyl, -C_{2-6}alkenyl, -$(CH_2CH_2O)_nR^a$, -$C(=O)R^a$,-$C(=O)OR^a$, -$C(=O)NR^aR^b$, -C_{1-6}alkyl-O-C_{1-6}alkyl, a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or

spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl and heterocycloalkyl groups have 1, 2, 3, or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group, and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2.

131. The compound of any one of Embodiments 1, 2, or 119-130, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^9 is $–CH_3$.

132. The compound of any one of Embodiments 1, 2, or 119-130, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^9 is $–CH_2CH_3$.

133. The compound of any one of Embodiments 1, 2, or 119-132, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is independently selected from H, C_{1-6}haloalkyl, C_{1-6}alkyl, -C_{2-6}alkenyl -$(CH_2CH_2O)_nR^a$, -SO_2R^a, -$C(=O)R^a$,-$C(=O)OR^a$, -$C(=O)NR^aR^b$, -NR^aR^b, -N=N=N, -C_{1-6}alkyl-O-C_{1-6}alkyl, a 6- to 12-membered aryl, a 6- to 12-membered heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl and heterocycloalkyl group have 1, 2, 3, or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group, and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2.

134. The compound of any one of Embodiments 1, 2, or 119-133, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is -C_{1-6}alkyl.

135. The compound of any one of Embodiments 1, 2, or 119-113, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is -C(=O)R^a.

136. The compound of any one of Embodiments 1, 2, or 119-133, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heterocycloalkyl group has 1, 2, 3 or 4 heteroatoms independently selected from O, N or S.

137. The compound of any one of Embodiments 1, 2, 119-133 or 136, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is a 3- to 12-membered monocyclic heterocycloalkyl group, wherein the heterocycloalkyl group has 1, 2, 3 or 4 heteroatoms independently selected from O or N.

138. The compound of any one of Embodiments 1, 2, 119-133, or 136-137, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein the 3- to 12-membered monocyclic heterocycloalkyl R^{9A} group can be unsubstituted or substituted with 1, 2, 3 or 4 R^{10} substituents independently selected from OH, halo, -NR^cR^d, -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -OC_{1-6}alkyl, -C_{1-6}alkyl-OH, -C_{1-6}alkyl-O-C_{1-6}alkyl, C_{1-6}haloalkyl, -O-haloC_{1-6}alkyl, -SO_2R^c, -CN, -C(=O)NR^cR^d, -C(=O)R^c, -OC(=O)R^a, -C(=O)OR^c, a 6- to 12-membered aryl, a 6- to 12-membered heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered

monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl, and heterocycloalkyl groups have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group , and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2.

139. The compound of any one of Embodiments 1, 2, 119-133, or 136-138, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein the 1, 2, 3 or 4 R^{10} substituents are independently selected from -C_{1-6}alkyl or a 3- to 12-membered monocyclic heterocycloalkyl group, wherein the heterocycloalkyl group has 1, 2, 3 or 4 heteroatoms independently selected from O, N or S.

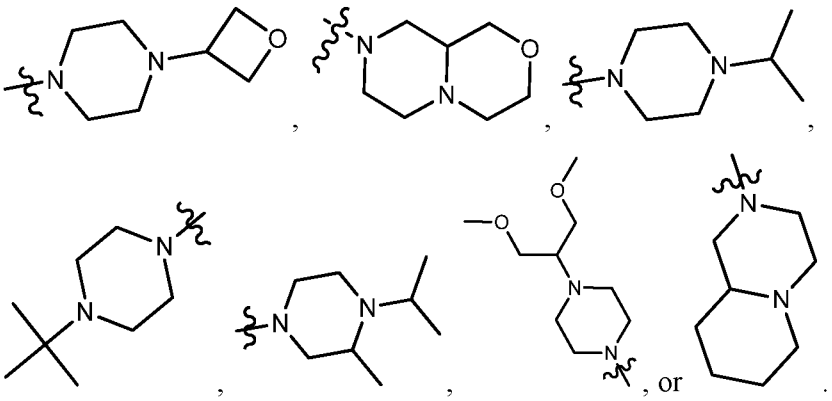
140. The compound of any one of Embodiments 1, 2, 119-133, or 136-139, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{10} is -C_{1-6}alkyl.

141. The compound of any one of Embodiments 1, 2, 119-133, or 136-139, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{10} is a 3- to 12-membered monocyclic heterocycloalkyl group, wherein the heterocycloalkyl group has 1, 2, 3 or 4 heteroatoms independently selected from O, N or S.

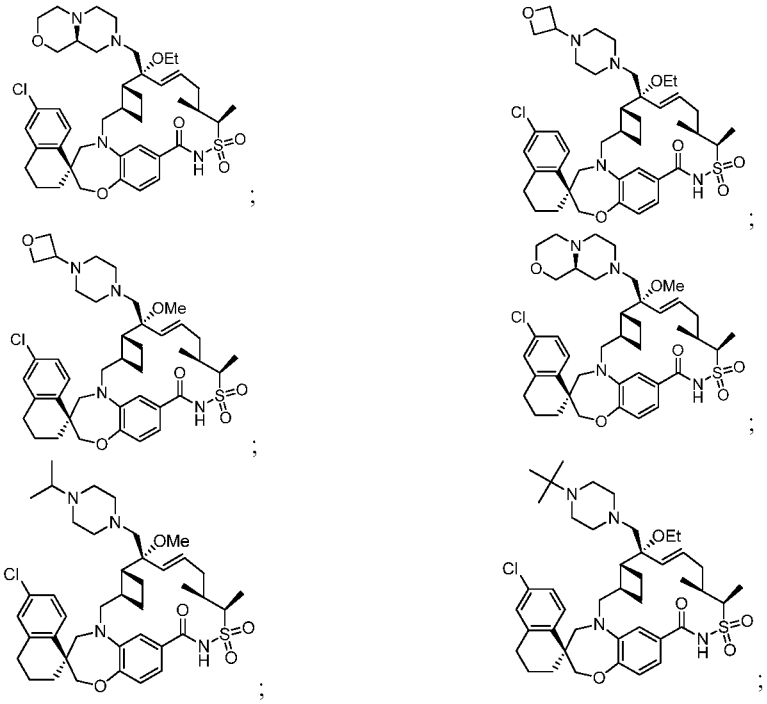
142. The compound of any one of Embodiments 1, 2, 119-133, or 136, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is a 5- to 12-membered bicyclic heterocycloalkyl group, wherein the heterocycloalkyl group has 1, 2, 3 or 4 heteroatoms independently selected from O or N.

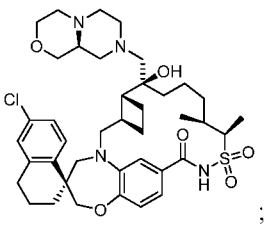
143. The compound of any one of Embodiments 68-70, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the

pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is independently selected from:



144. Another embodiment of the present invention comprises the compound of Embodiment 1, wherein the compound is selected from:

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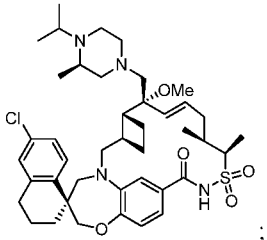
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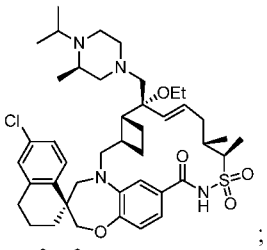
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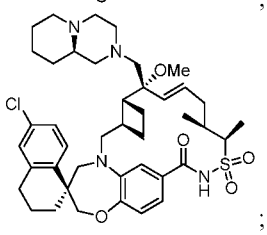
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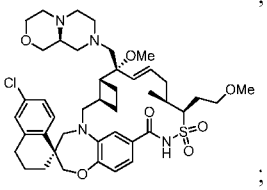
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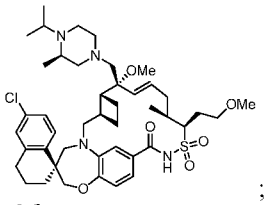
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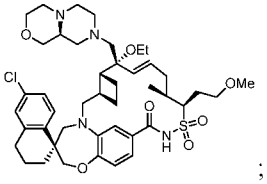
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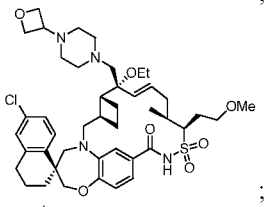
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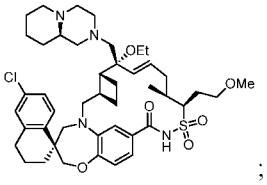
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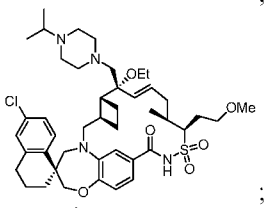
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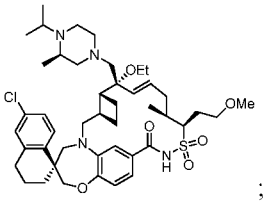
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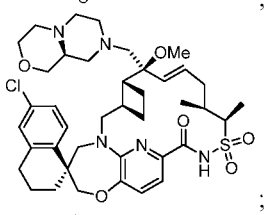
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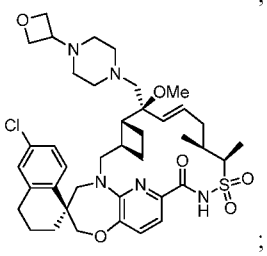
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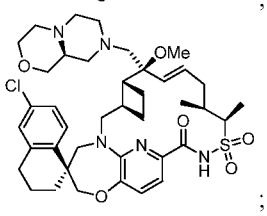
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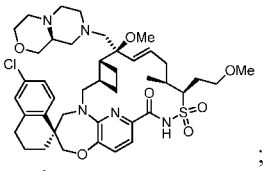
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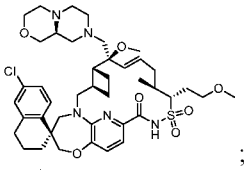
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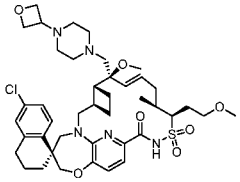
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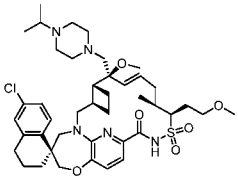
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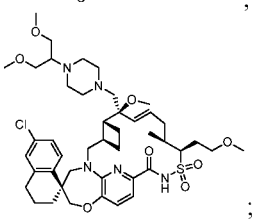
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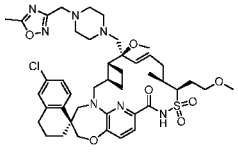
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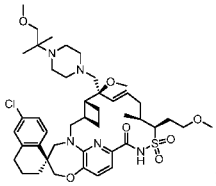
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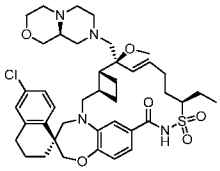
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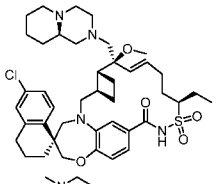
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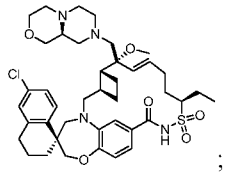
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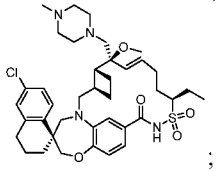
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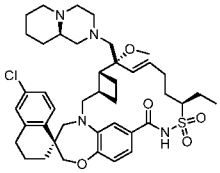
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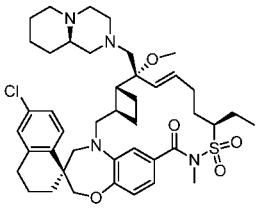
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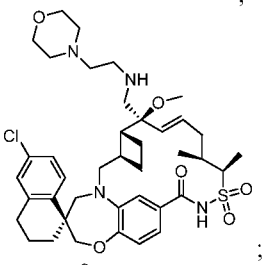
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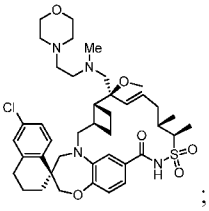
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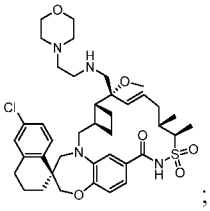
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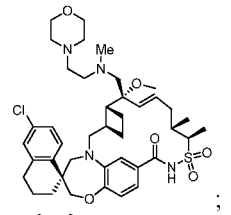
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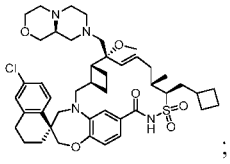
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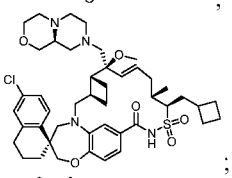
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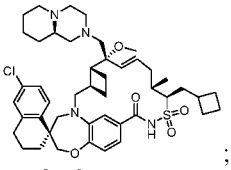
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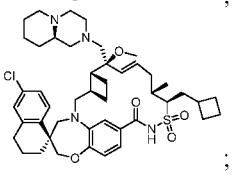
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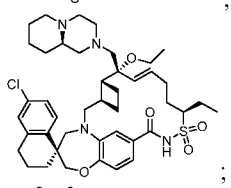
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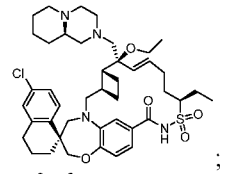
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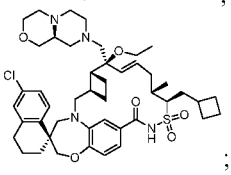
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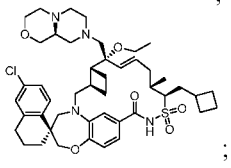
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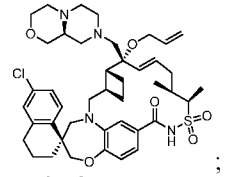
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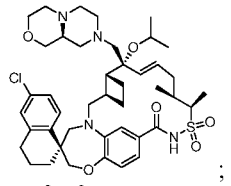
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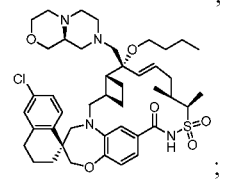
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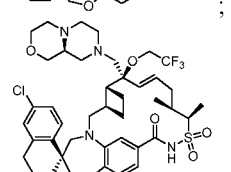
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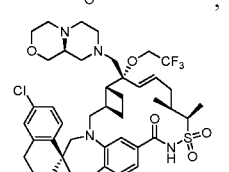
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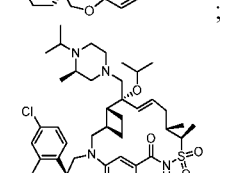
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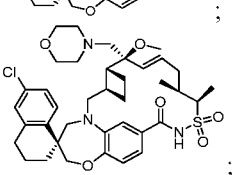
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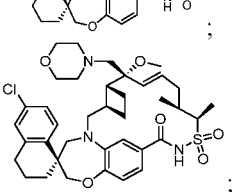
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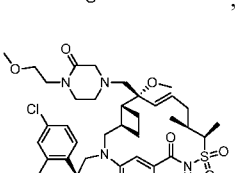
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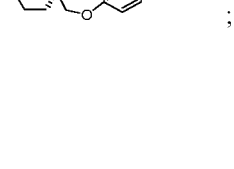
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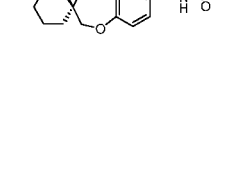
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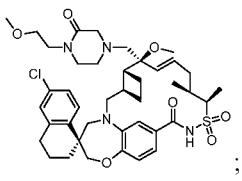
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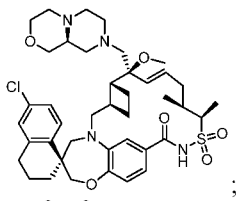
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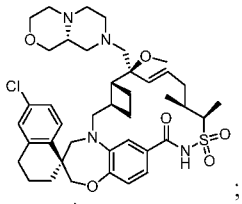
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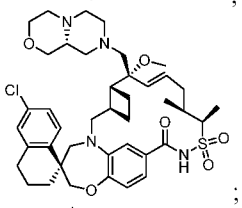
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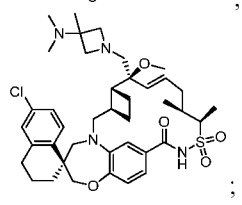
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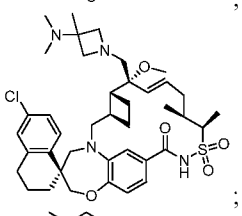
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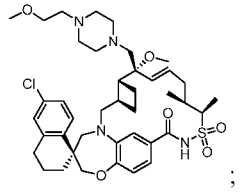
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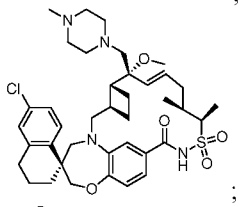
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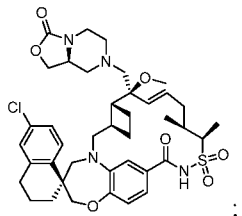
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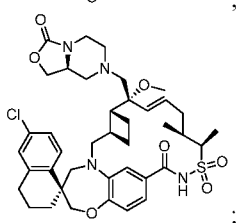
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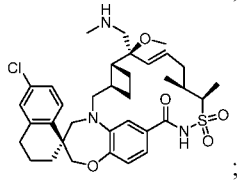
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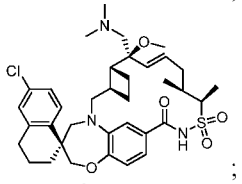
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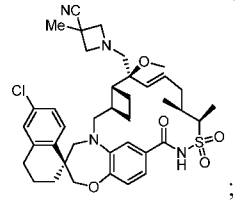
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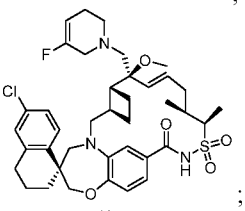
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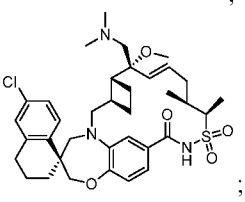
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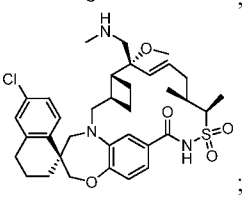
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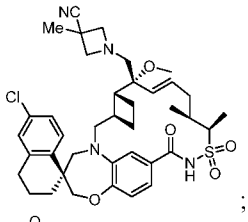
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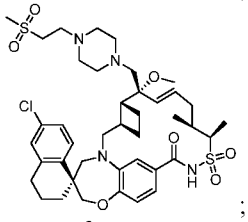
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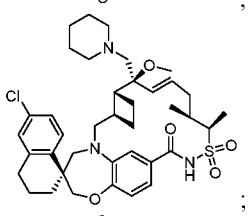
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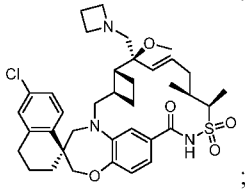
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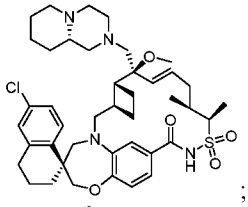
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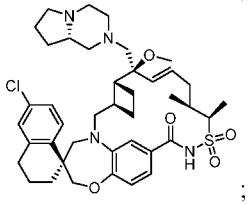
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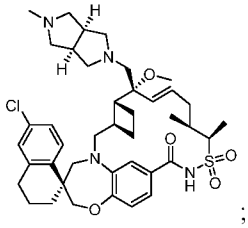
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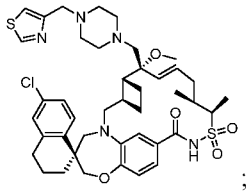
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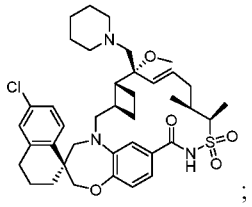
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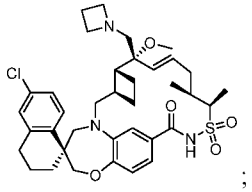
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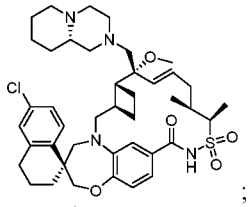
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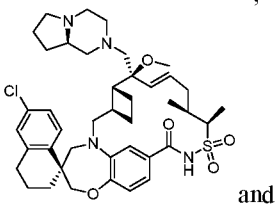
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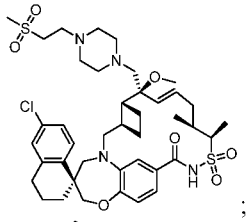
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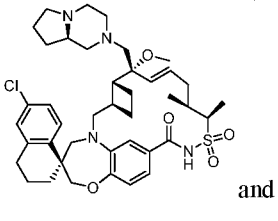
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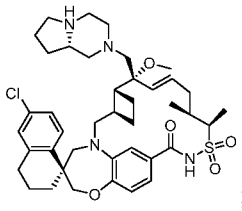
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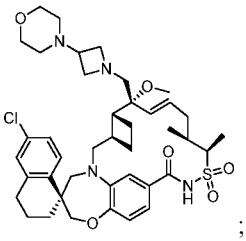
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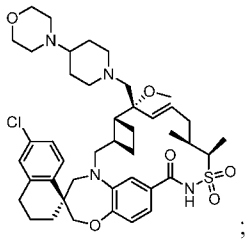
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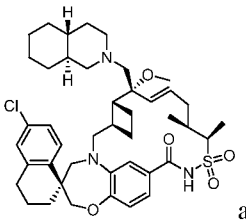
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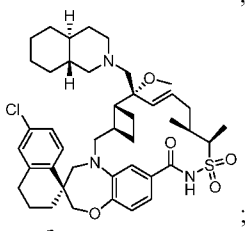
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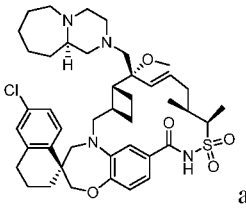
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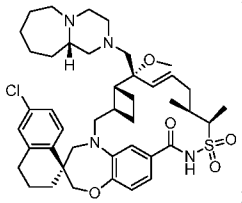
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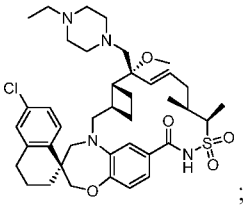
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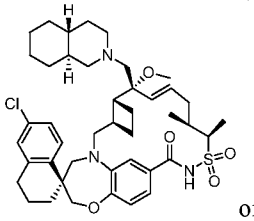
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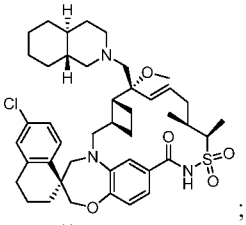
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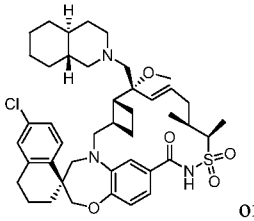
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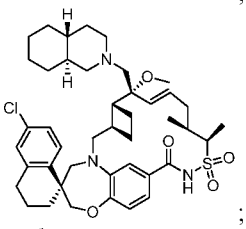
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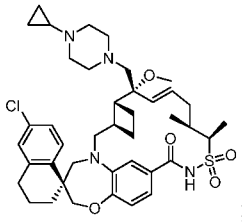
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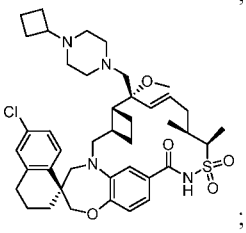
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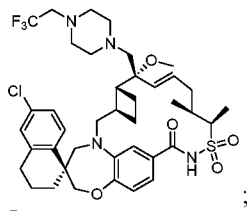
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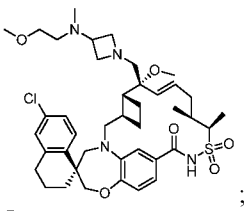
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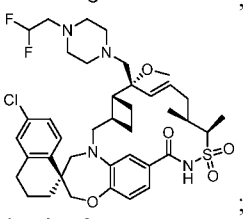
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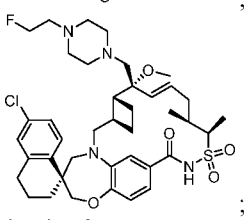
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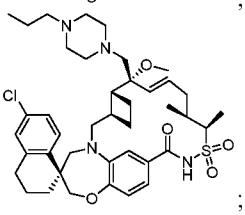
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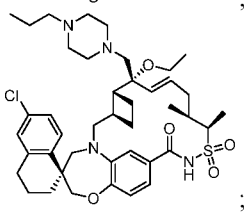
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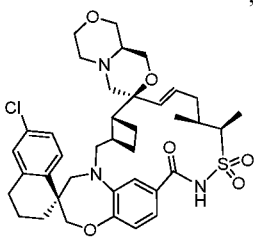
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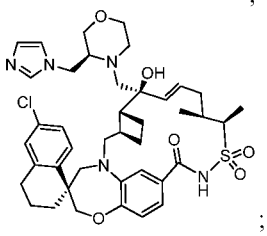
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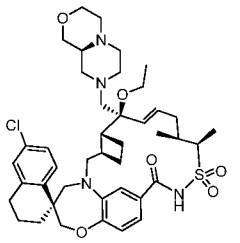
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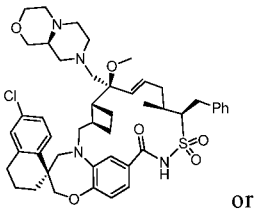
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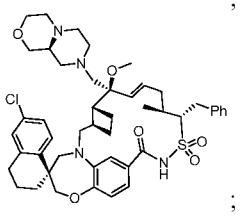
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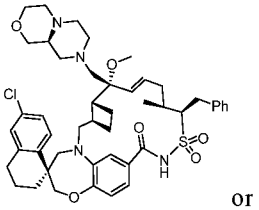
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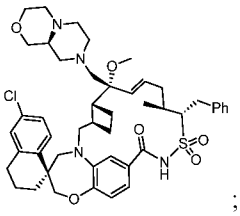
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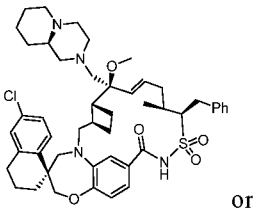
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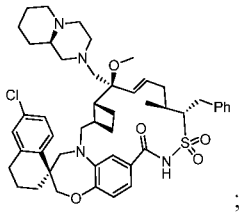
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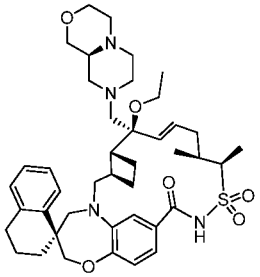
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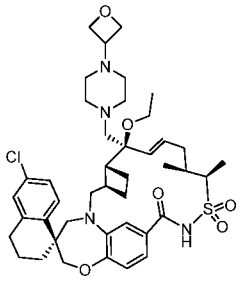
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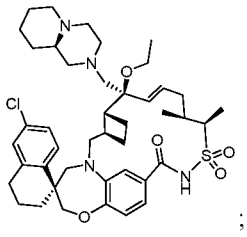
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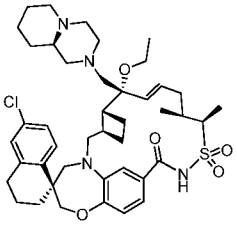
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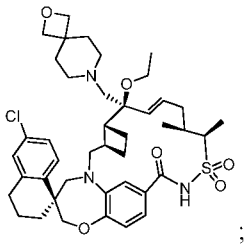
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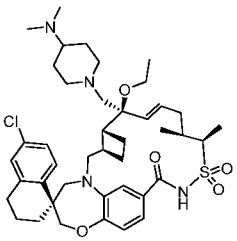
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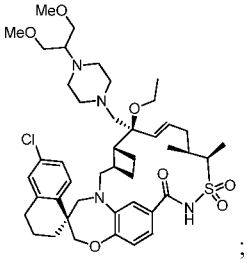
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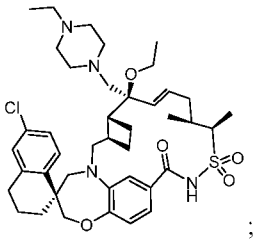
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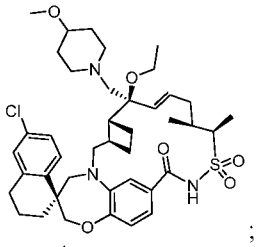
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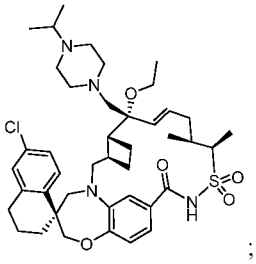
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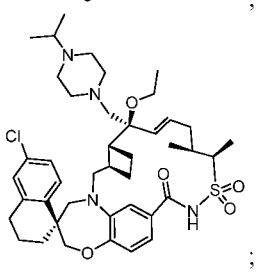
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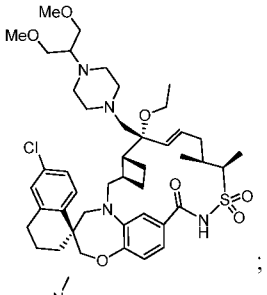
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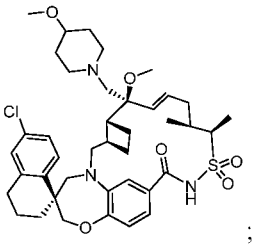
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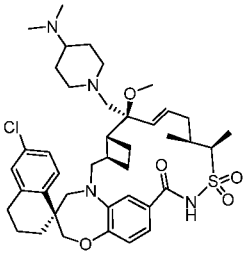
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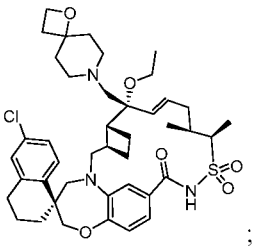
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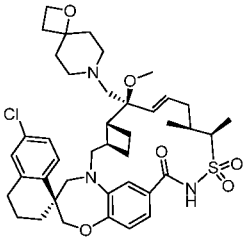
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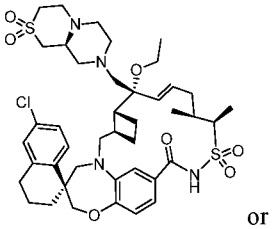
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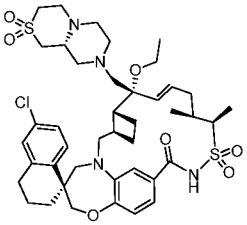
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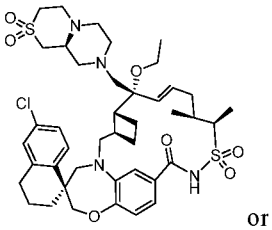
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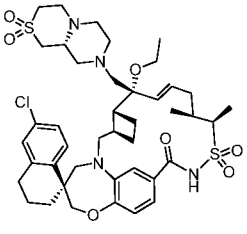
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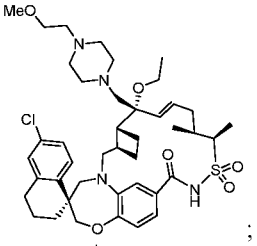
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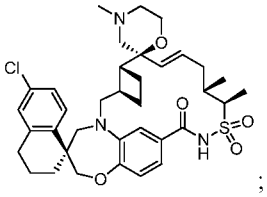
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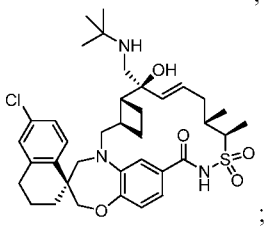
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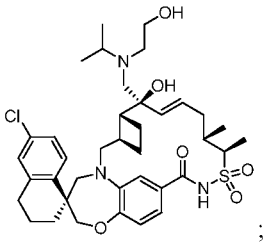
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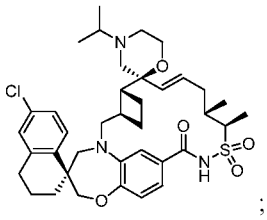
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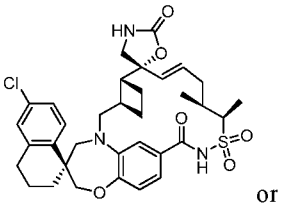
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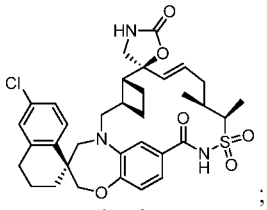
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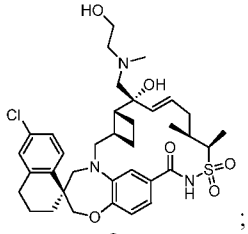
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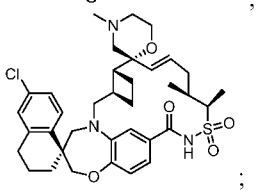
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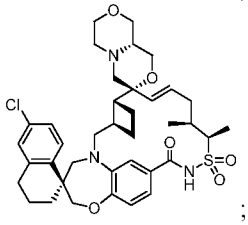
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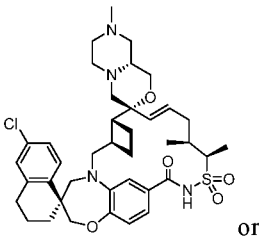
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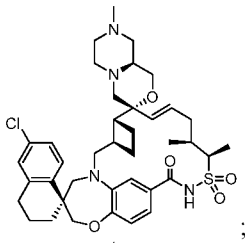
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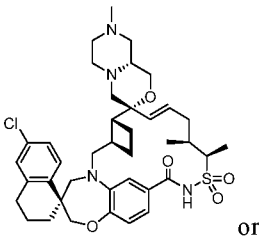
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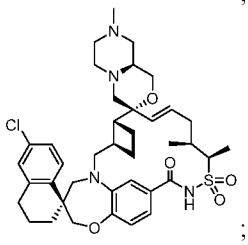
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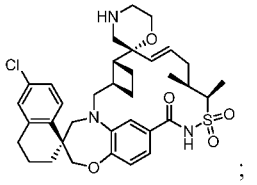
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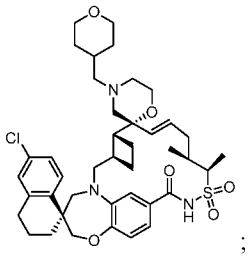
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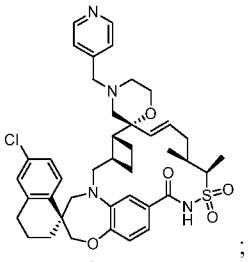
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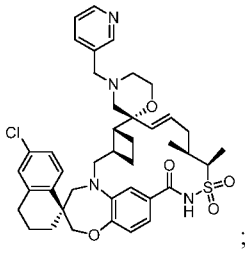
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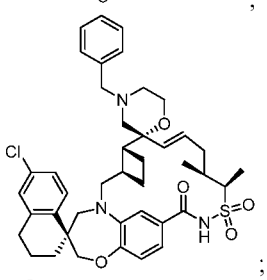
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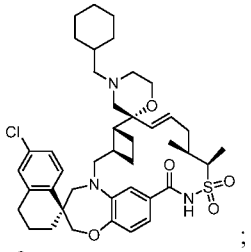
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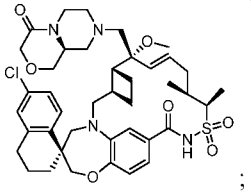
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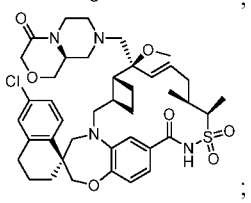
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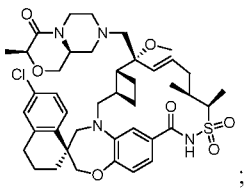
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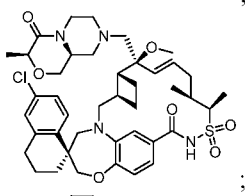
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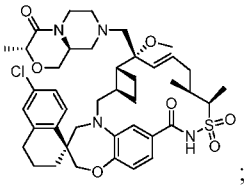
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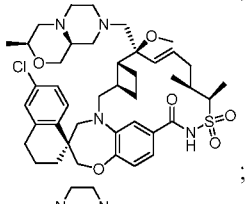
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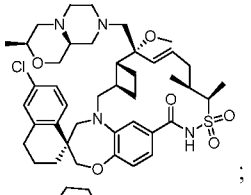
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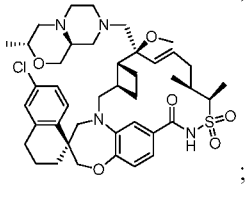
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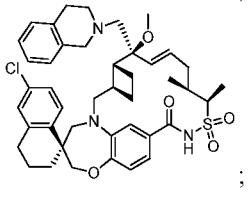
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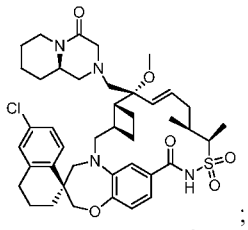
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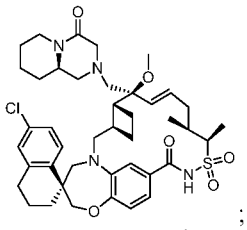
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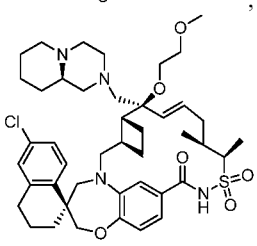
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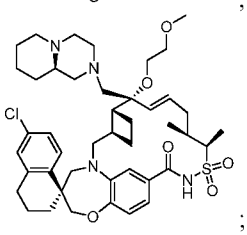
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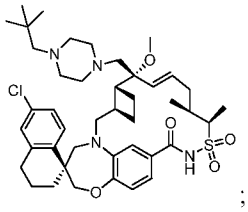
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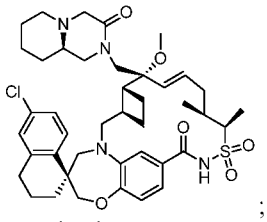
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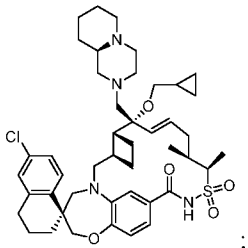
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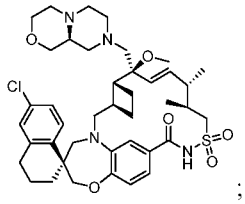
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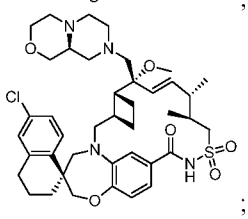
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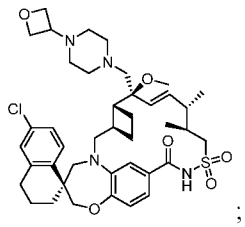
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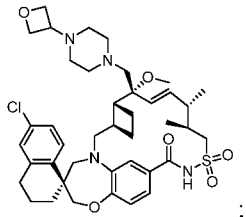
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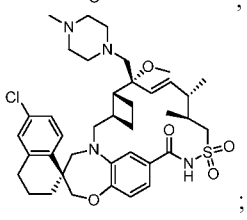
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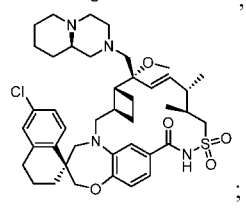
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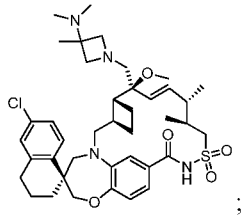
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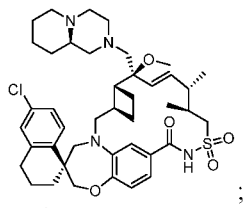
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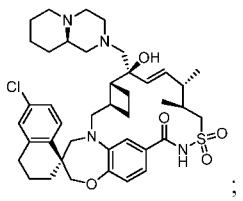
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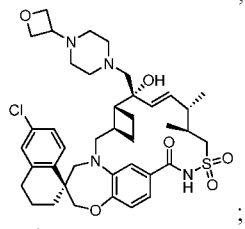
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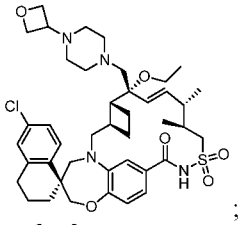
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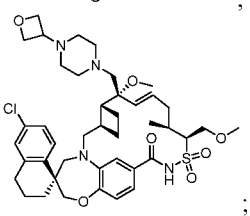
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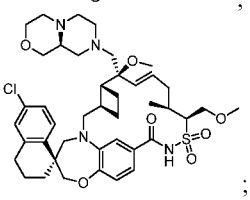
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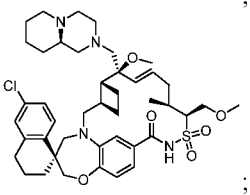
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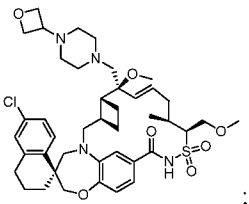
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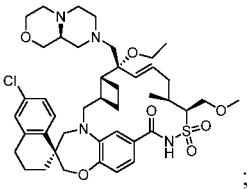
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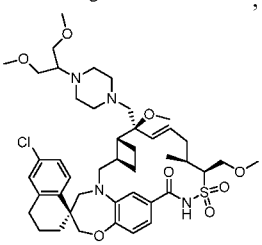
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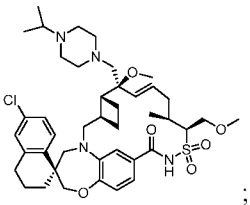
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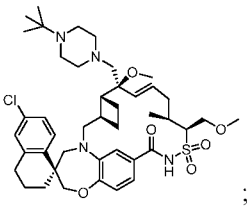
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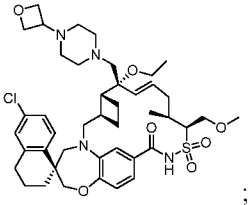
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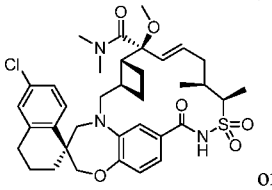
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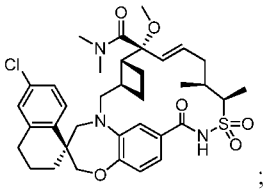
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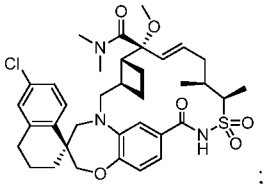
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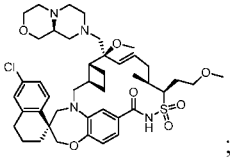
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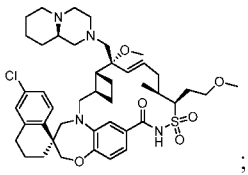
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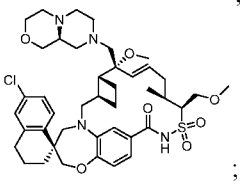
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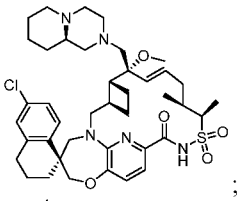
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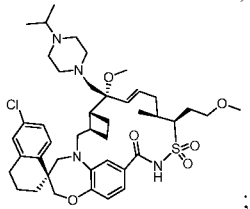
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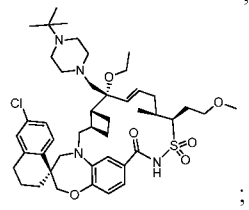
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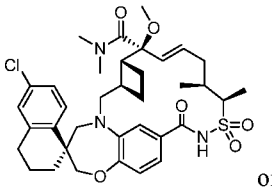
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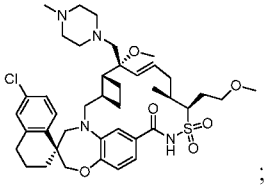
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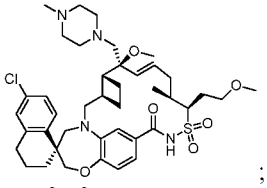
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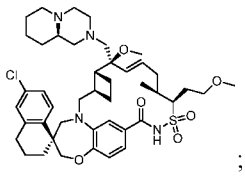
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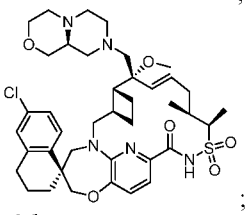
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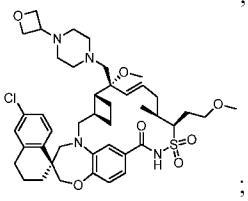
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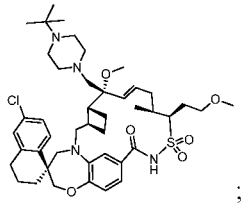
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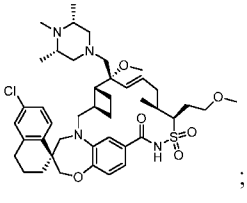
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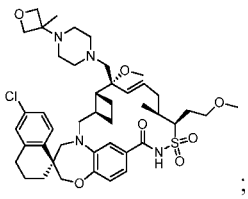
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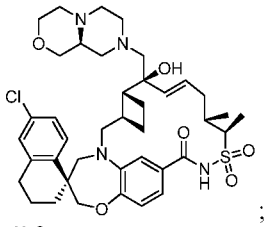
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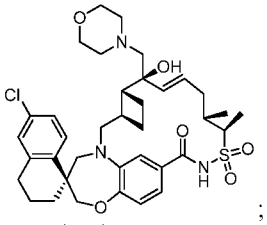
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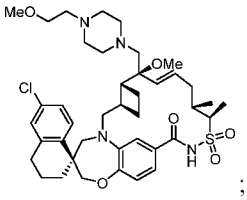
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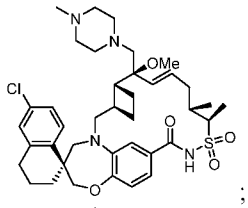
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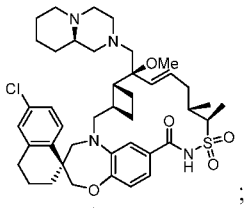
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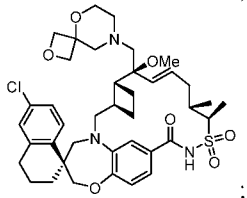
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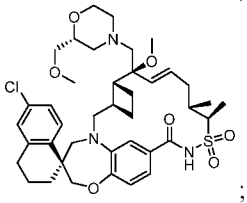
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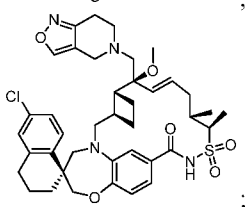
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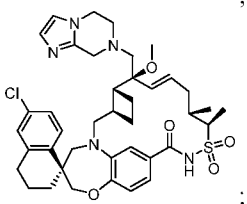
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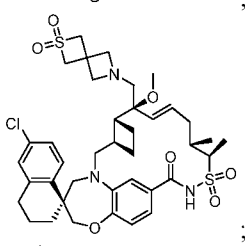
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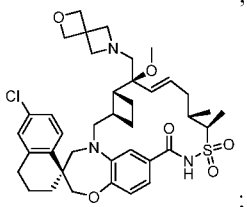
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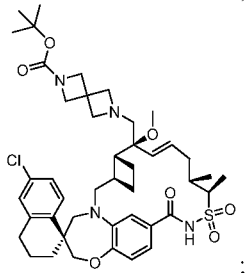
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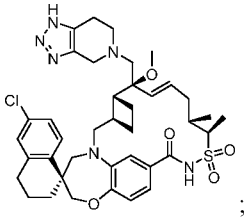
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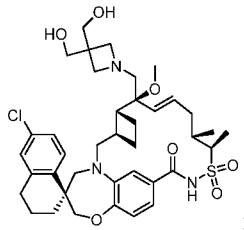
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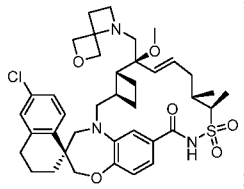
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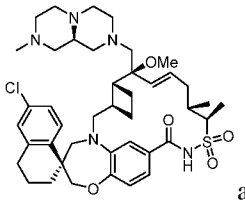
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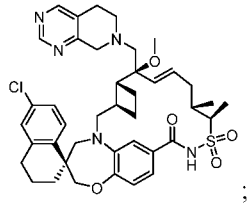
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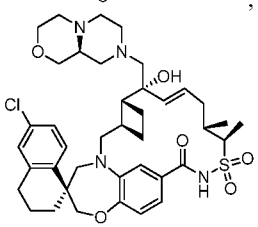
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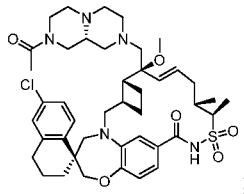
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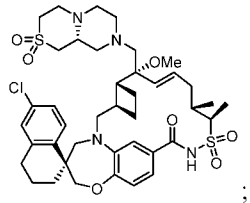
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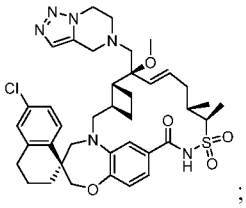
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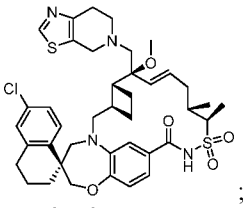
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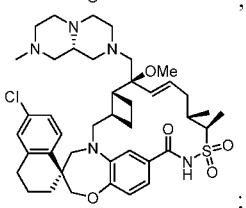
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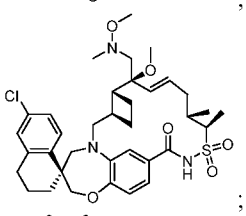
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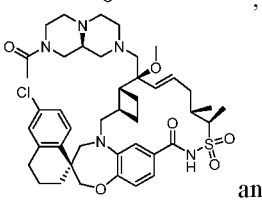
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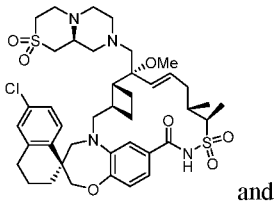
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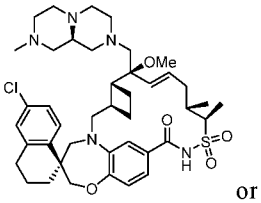
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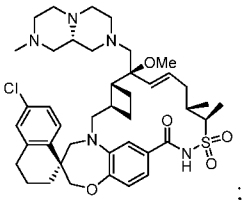
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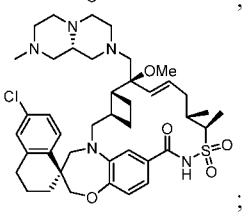
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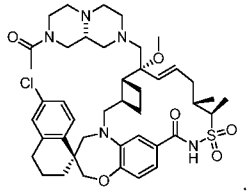
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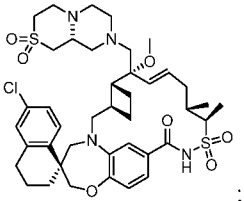
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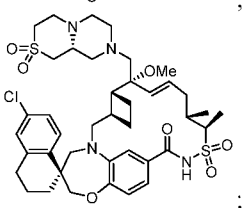
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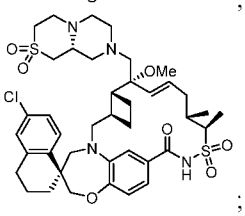
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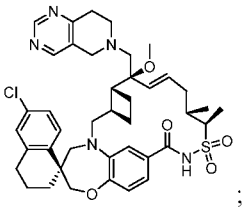
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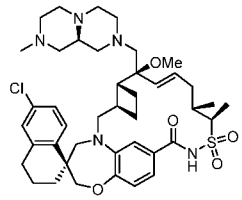
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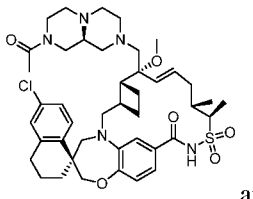
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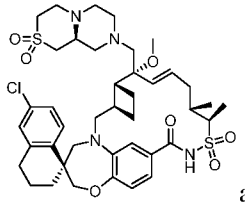
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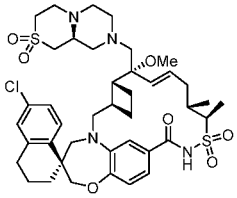
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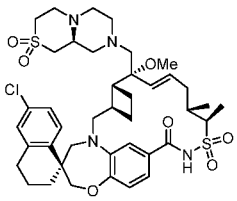
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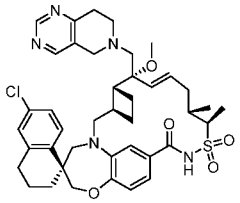
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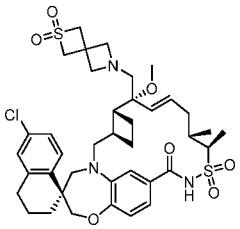
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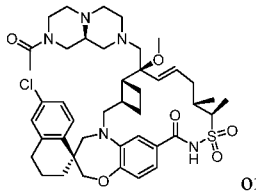
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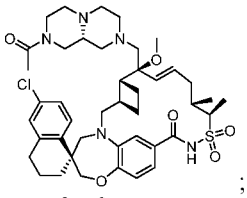
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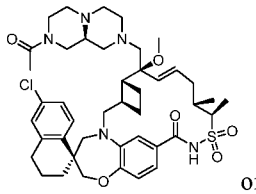
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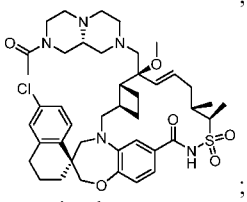
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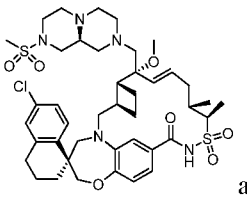
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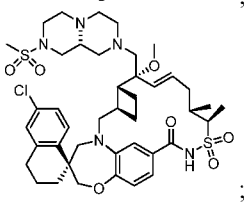
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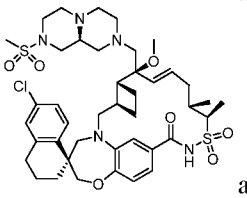
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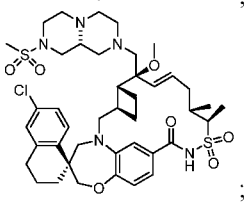
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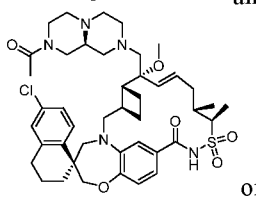
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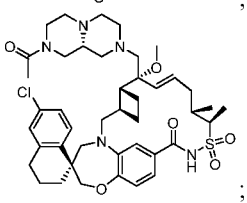
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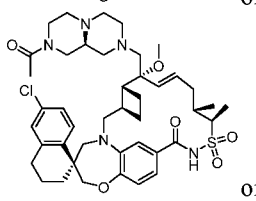
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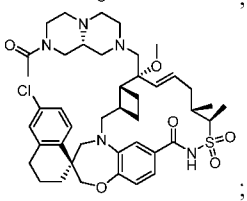
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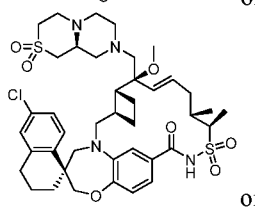
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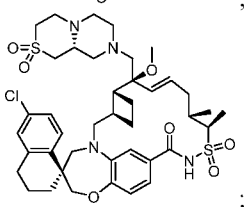
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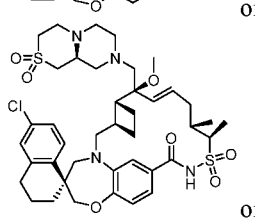
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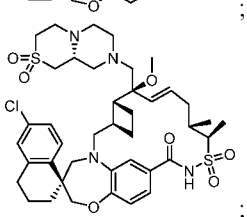
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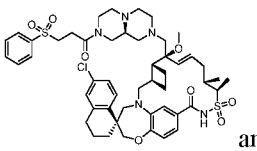
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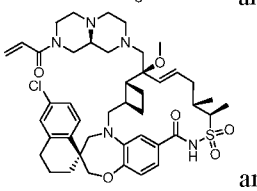
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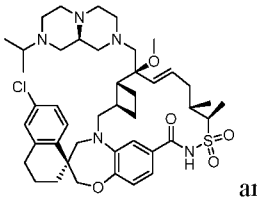
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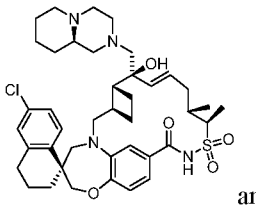
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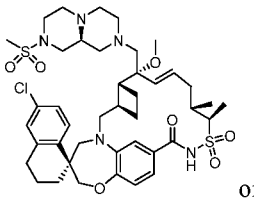
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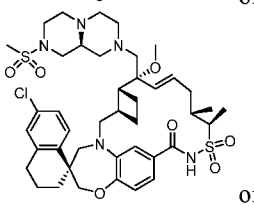
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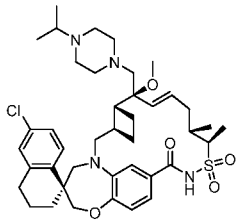
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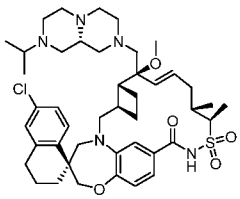
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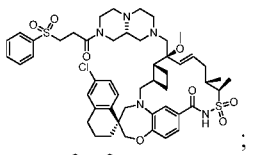
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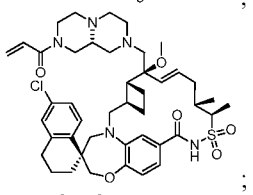
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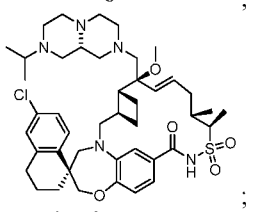
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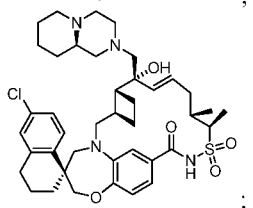
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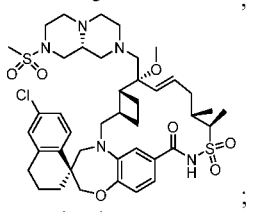
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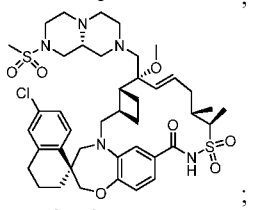
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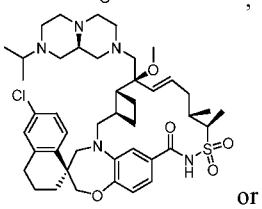
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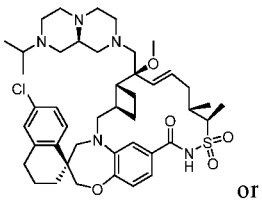
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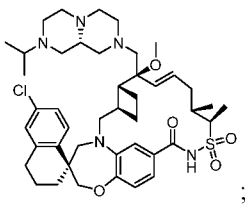
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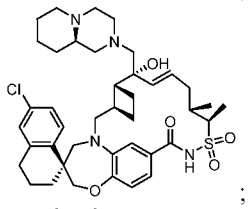
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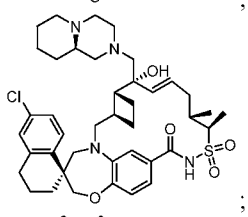
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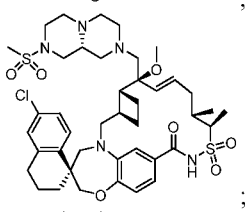
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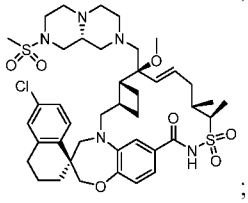
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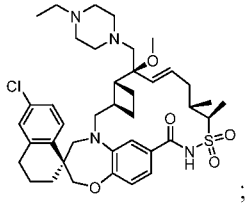
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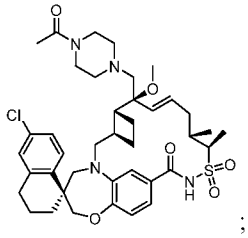
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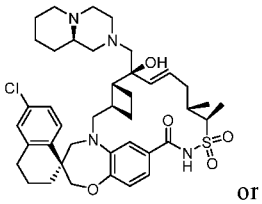
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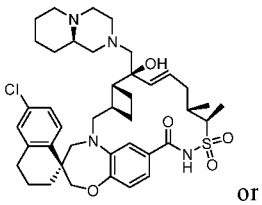
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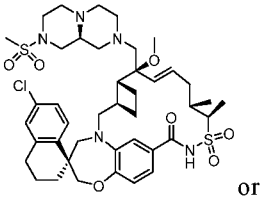
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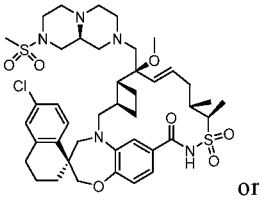
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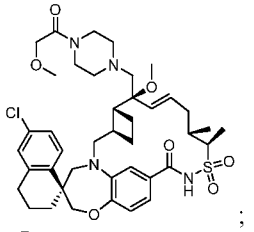
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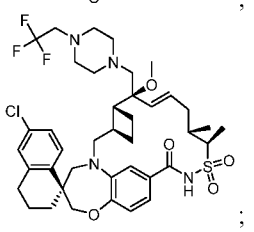
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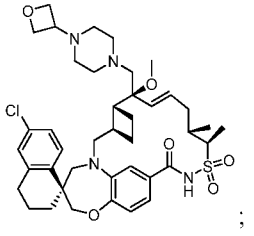
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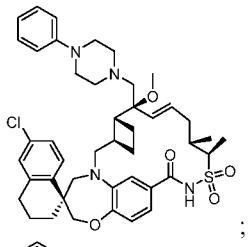
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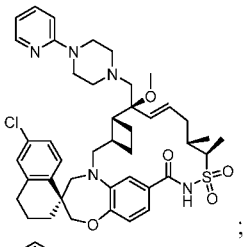
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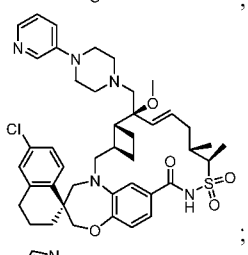
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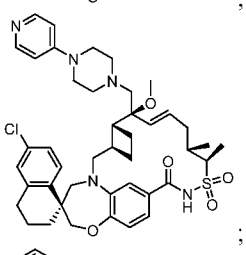
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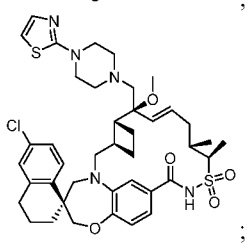
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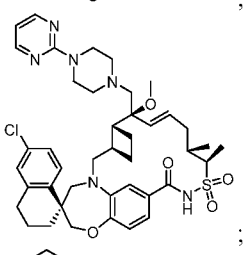
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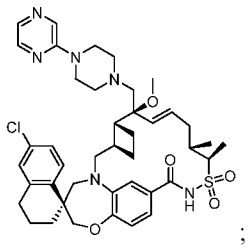
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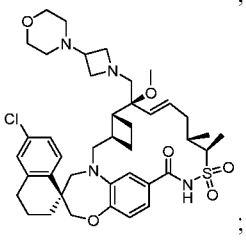
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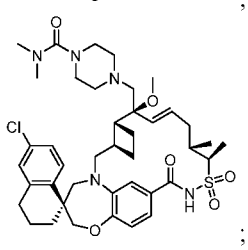
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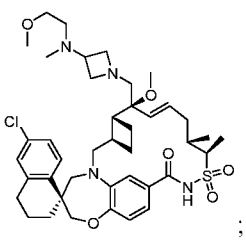
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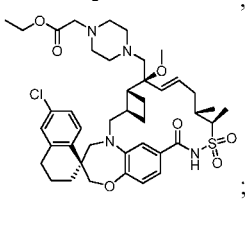
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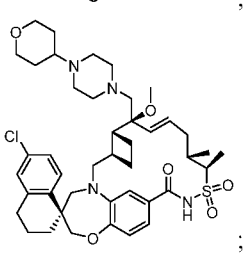
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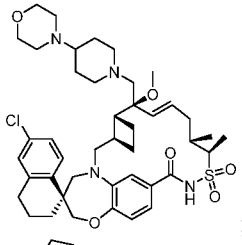
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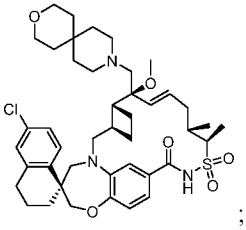
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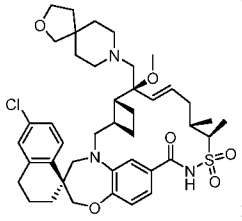
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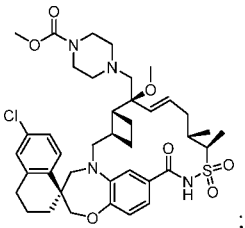
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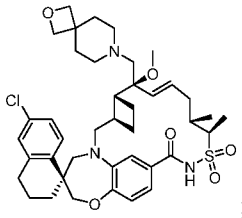
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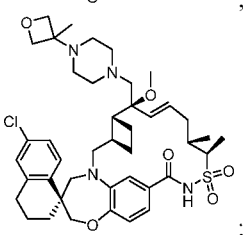
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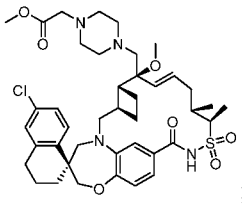
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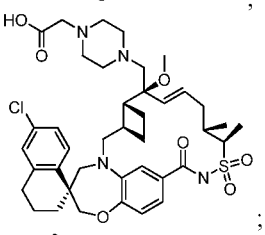
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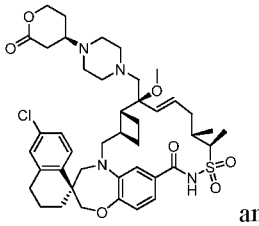
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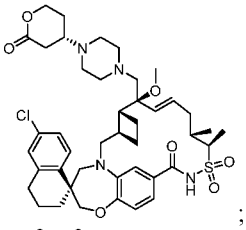
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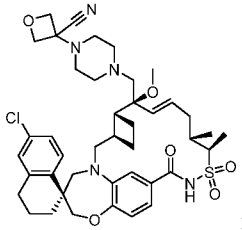
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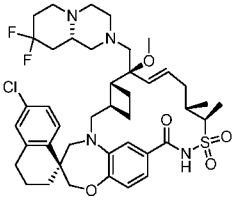
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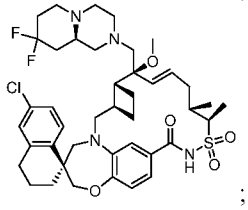
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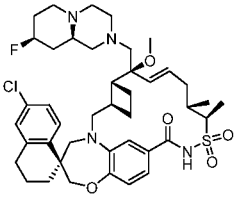
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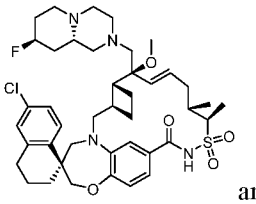
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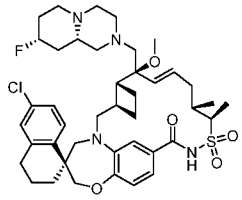
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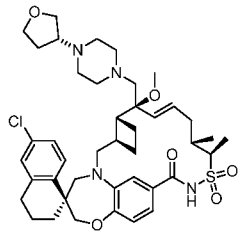
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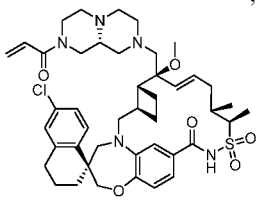
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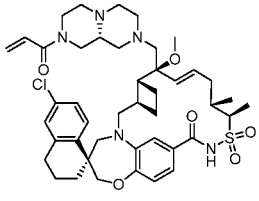
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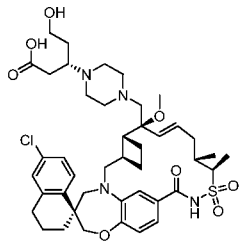
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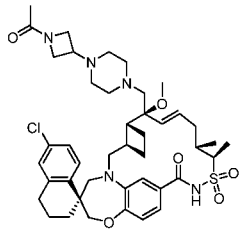
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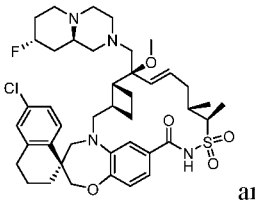
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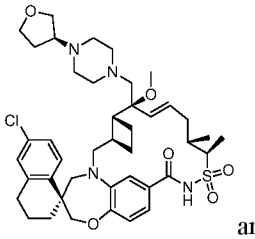
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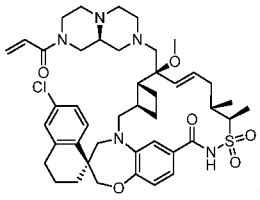
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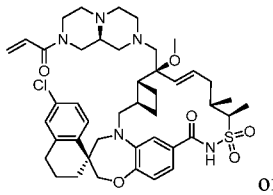
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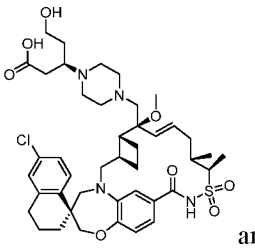
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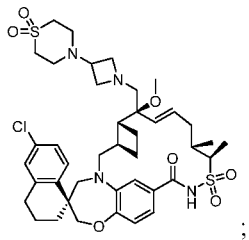
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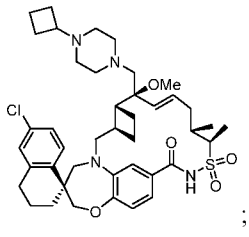
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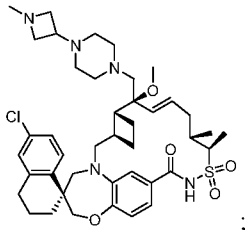
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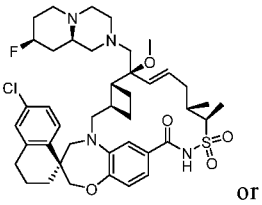
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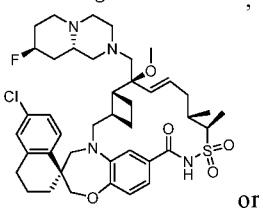
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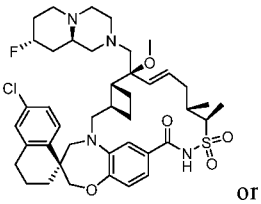
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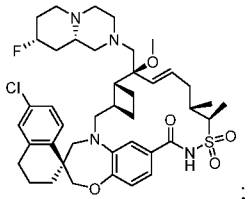
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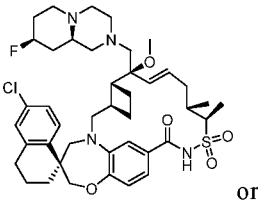
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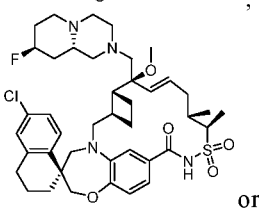
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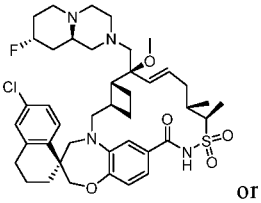
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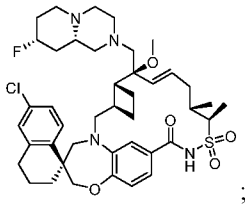
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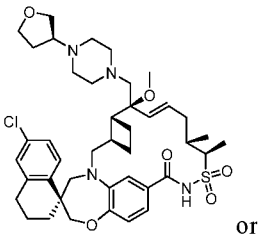
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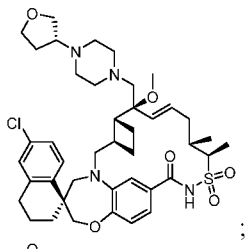
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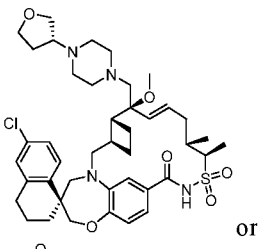
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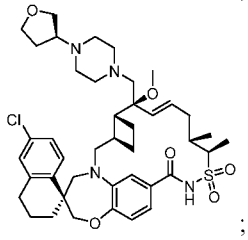
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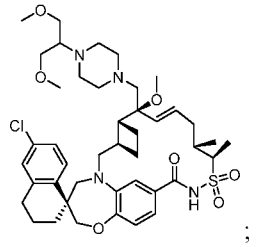
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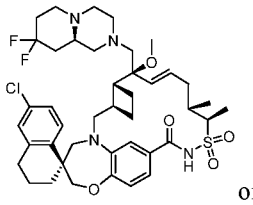
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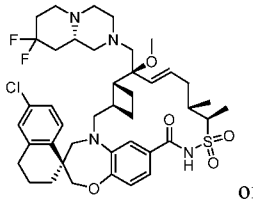
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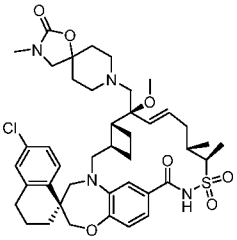
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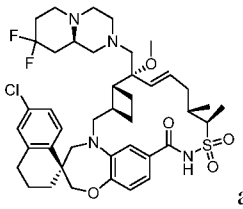
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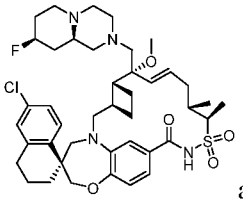
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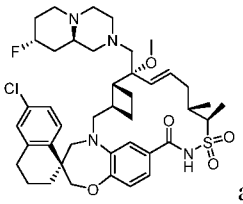
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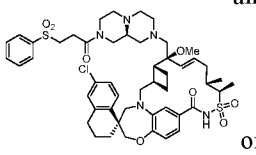
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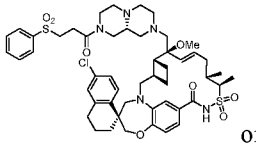
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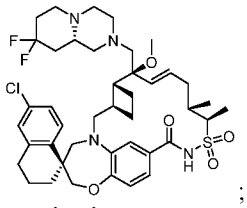
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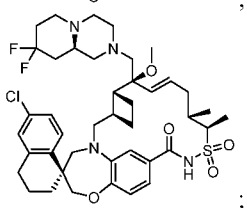
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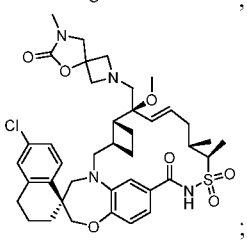
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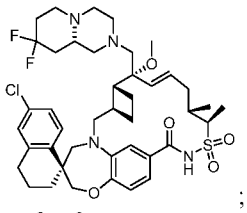
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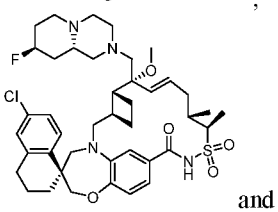
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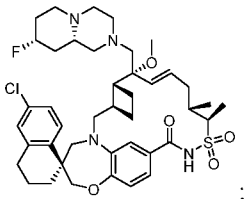
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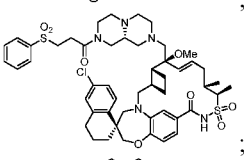
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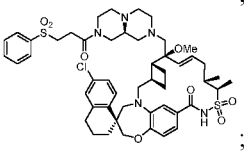
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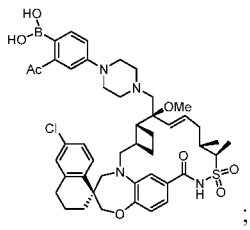
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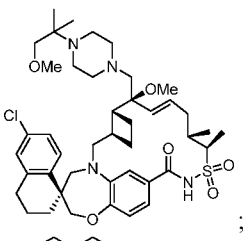
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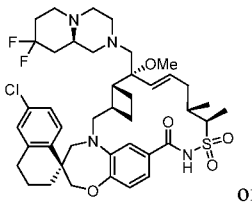
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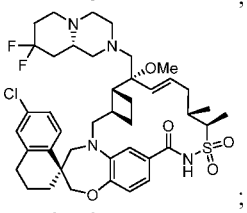
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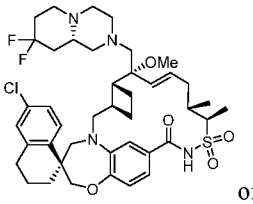
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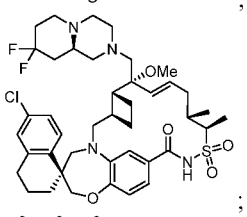
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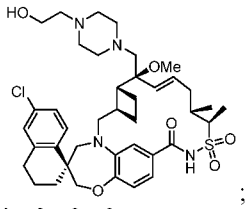
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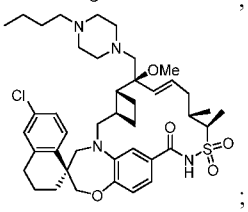
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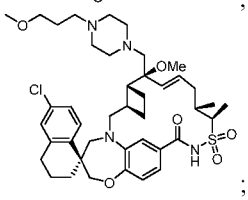
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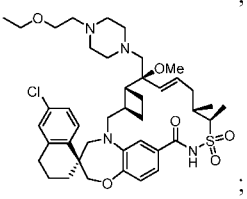
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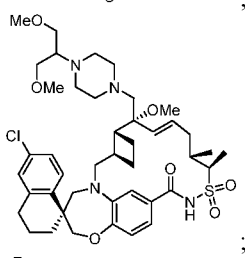
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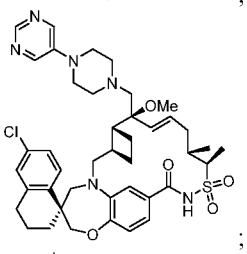
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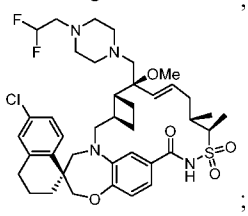
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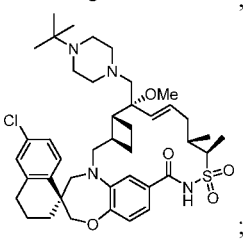
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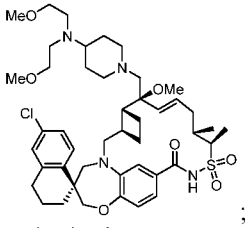
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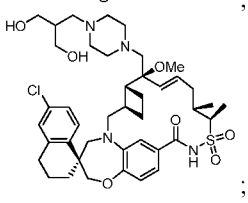
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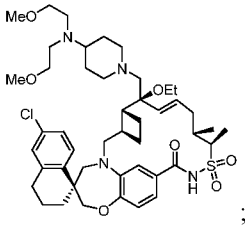
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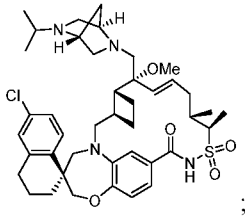
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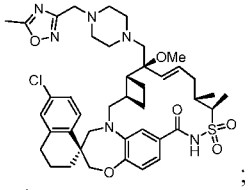
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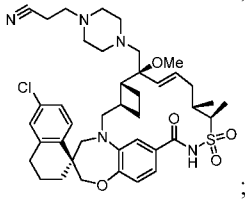
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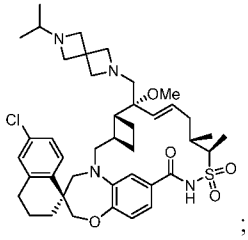
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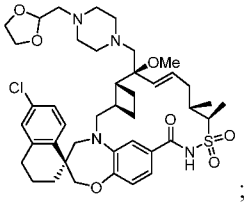
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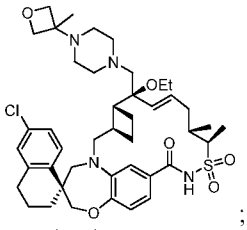
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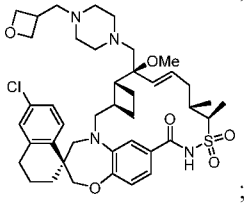
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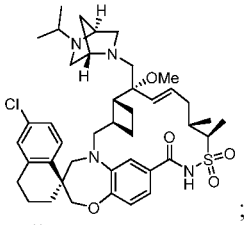
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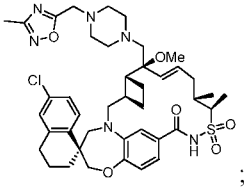
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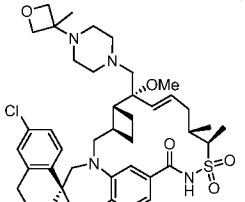
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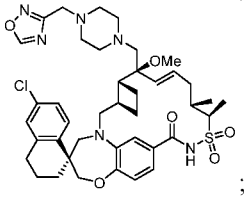
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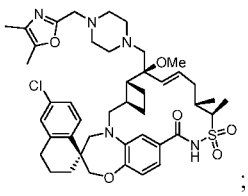
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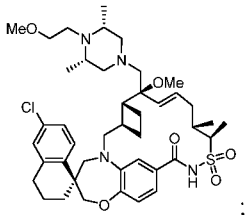
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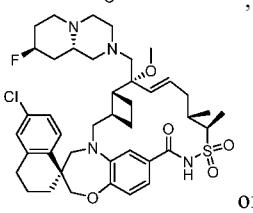
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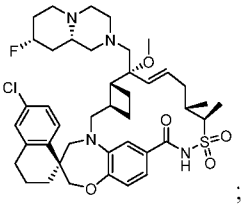
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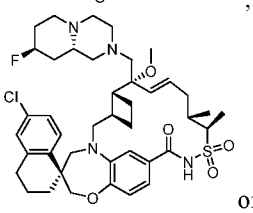
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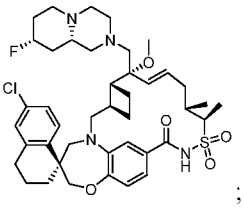
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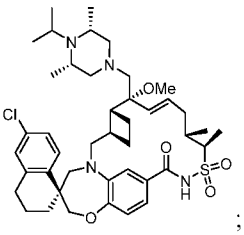
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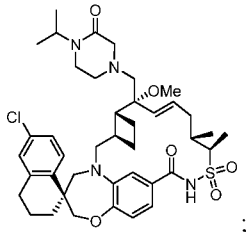
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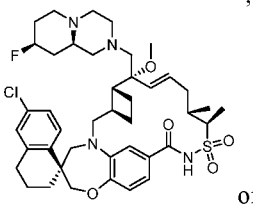
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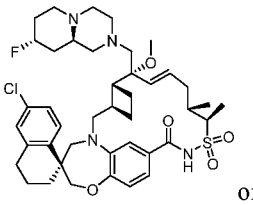
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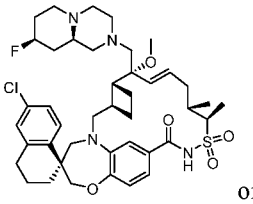
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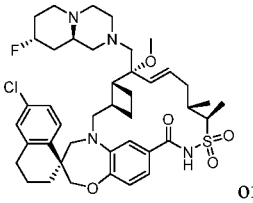
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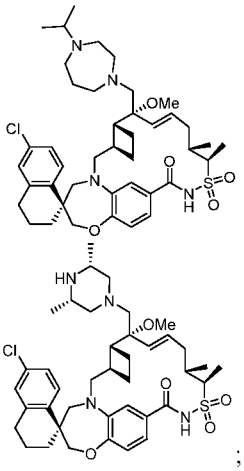
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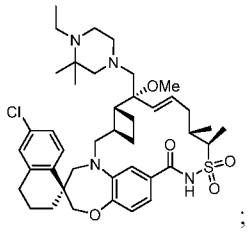
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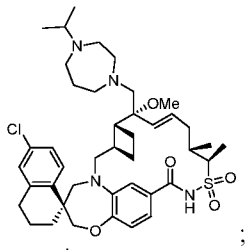
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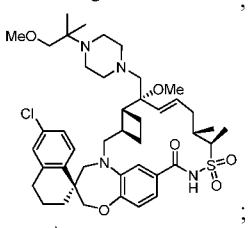
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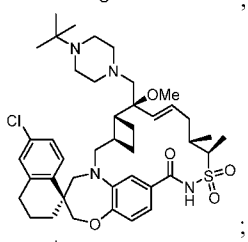
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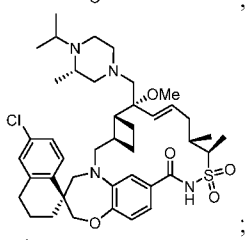
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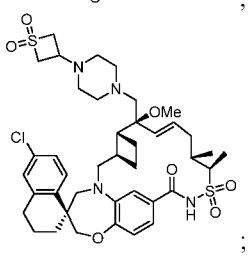
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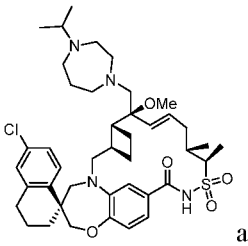
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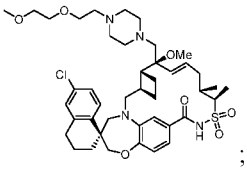
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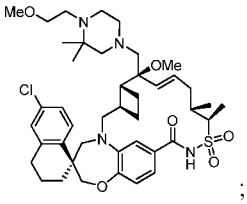
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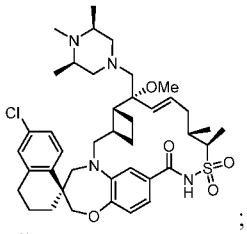
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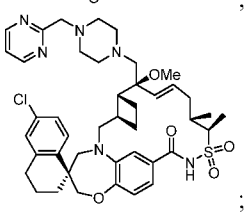
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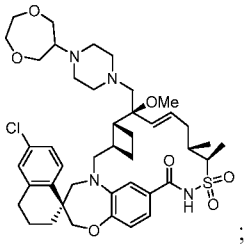
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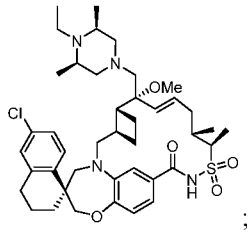
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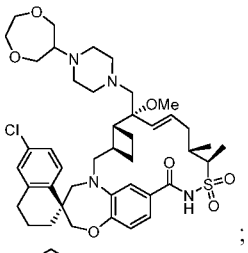
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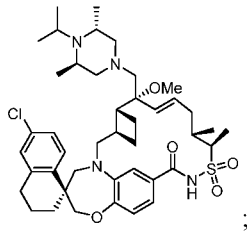
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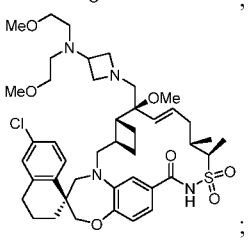
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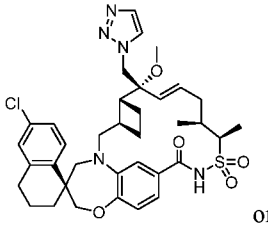
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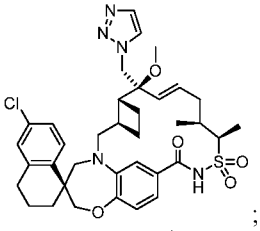
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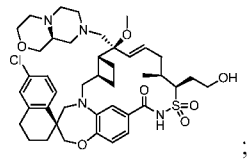
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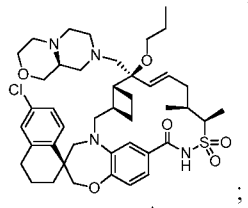
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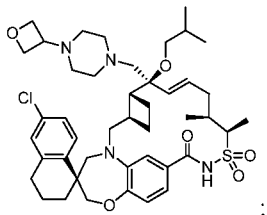
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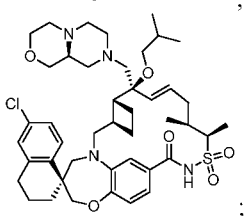
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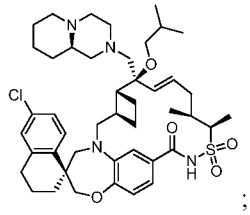
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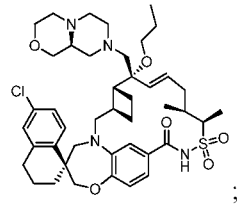
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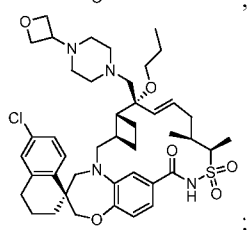
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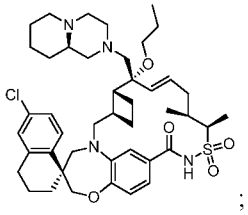
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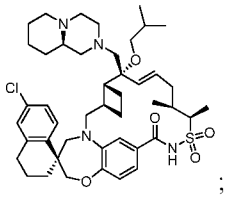
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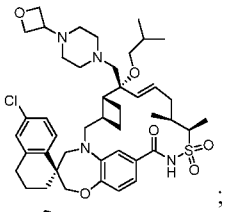
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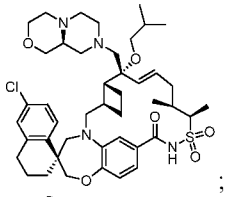
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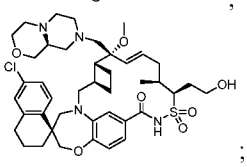
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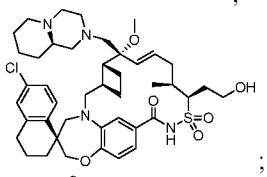
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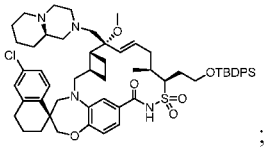
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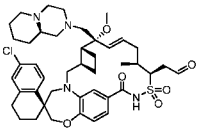
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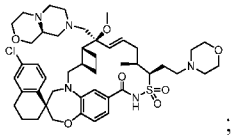
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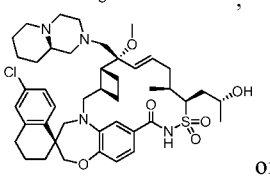
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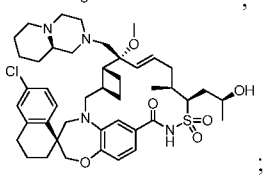
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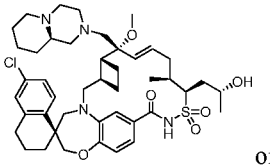
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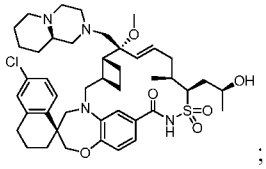
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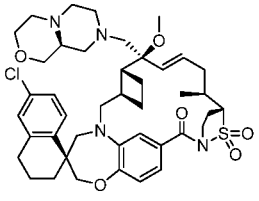
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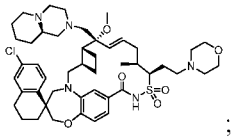
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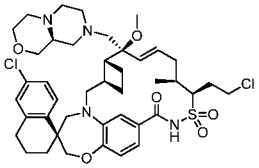
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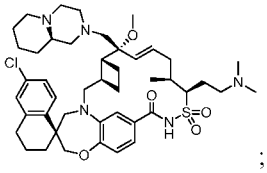
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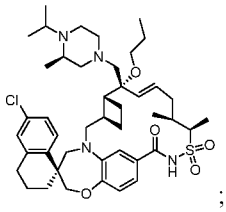
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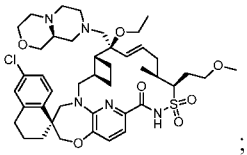
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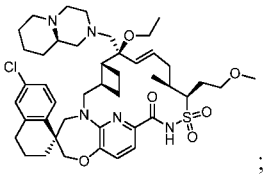
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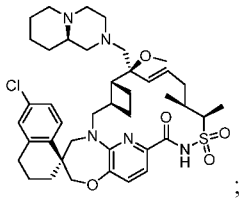
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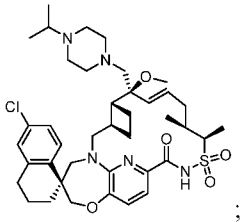
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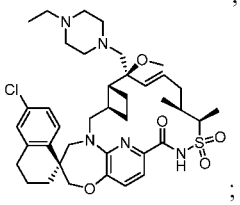
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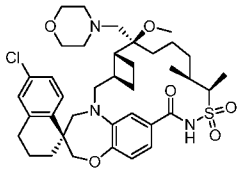
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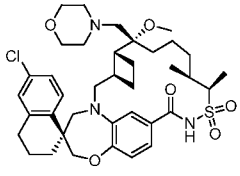
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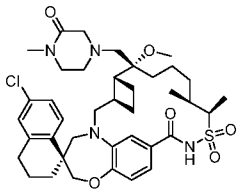
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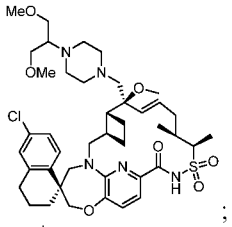
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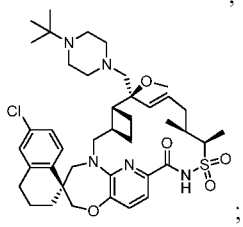
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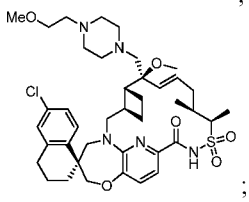
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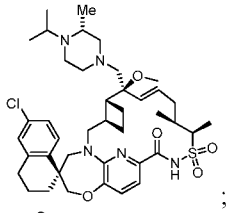
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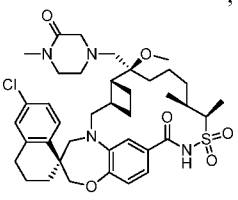
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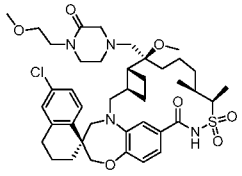
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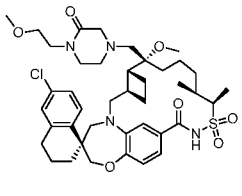
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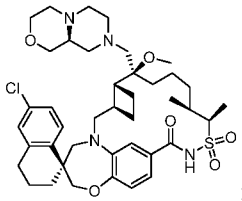
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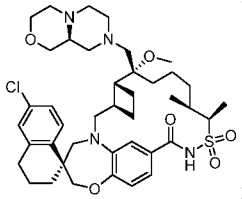
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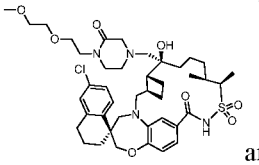
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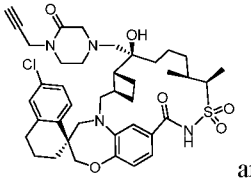
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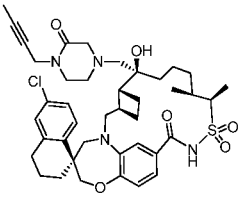
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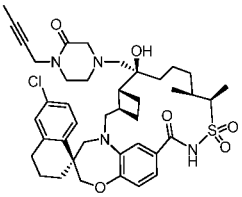
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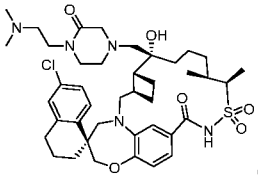
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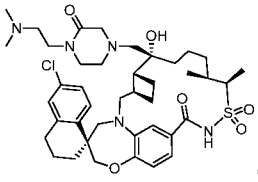
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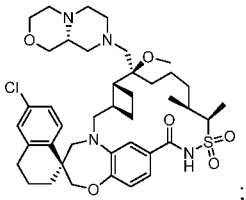
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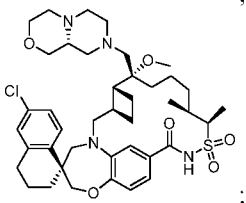
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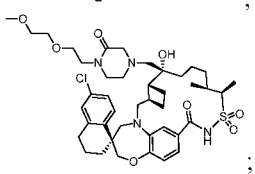
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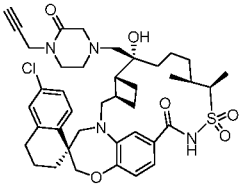
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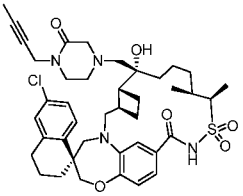
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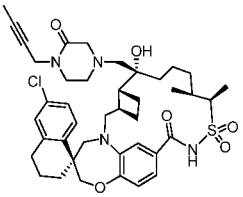
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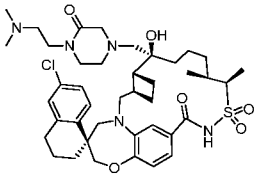
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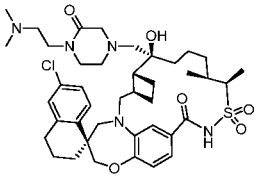
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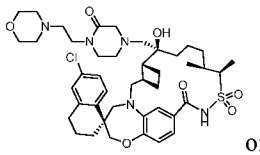
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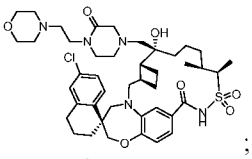
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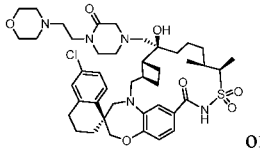
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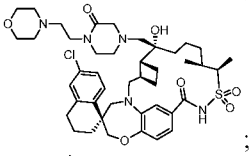
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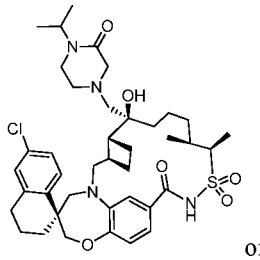
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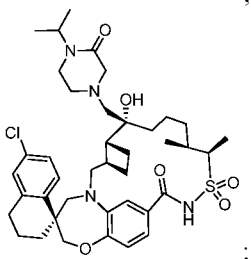
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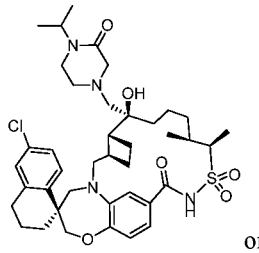
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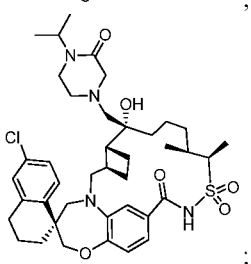
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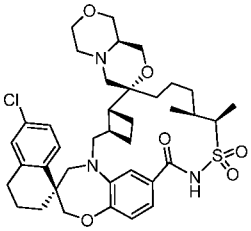
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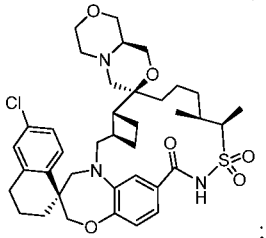
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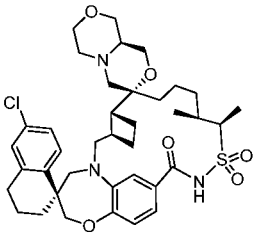
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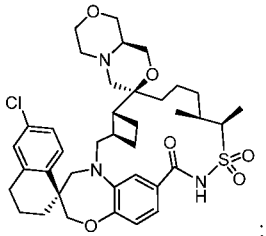
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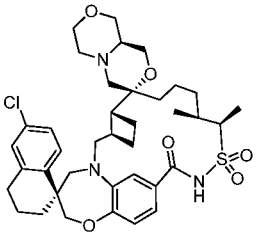
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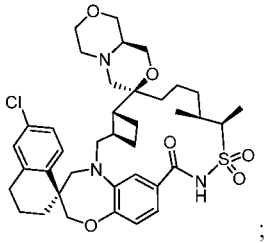
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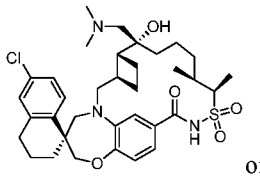
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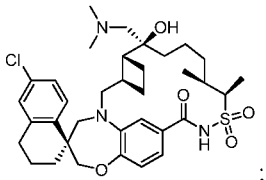
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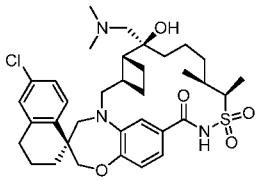
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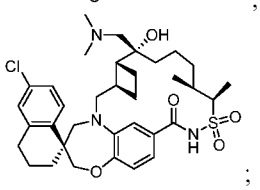
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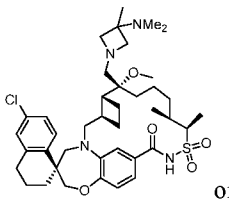
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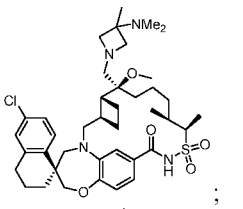
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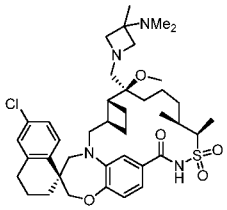
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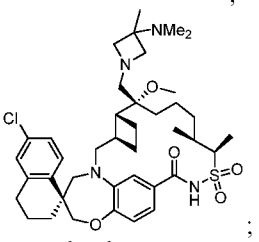
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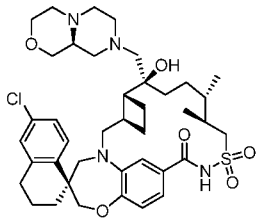
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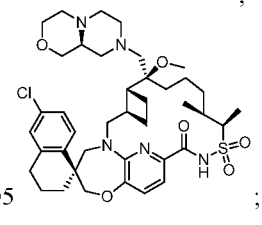
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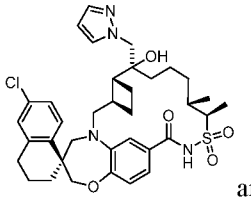
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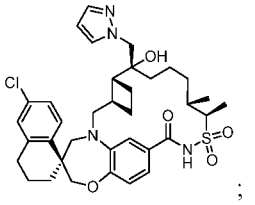
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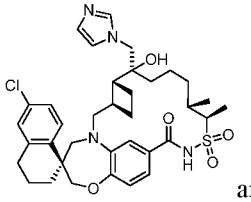
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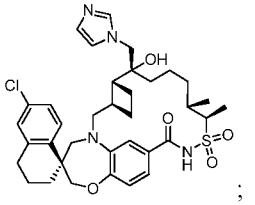
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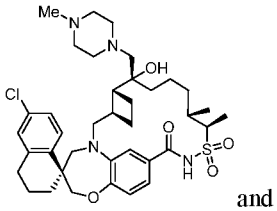
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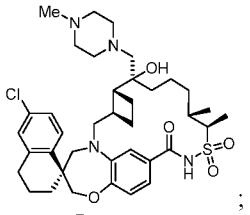
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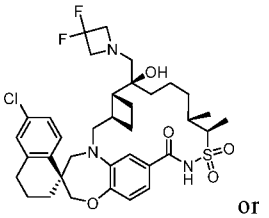
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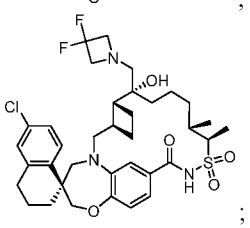
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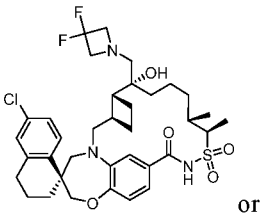
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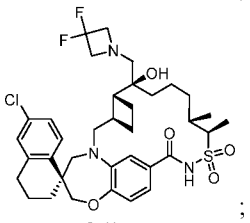
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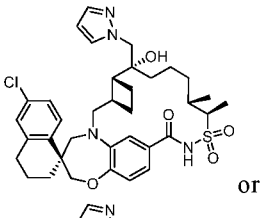
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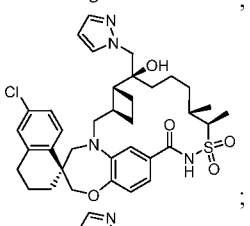
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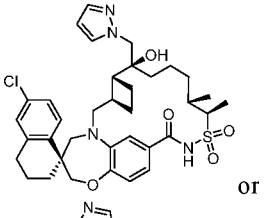
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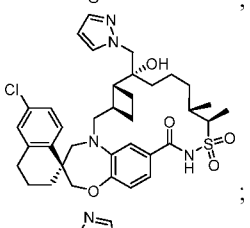
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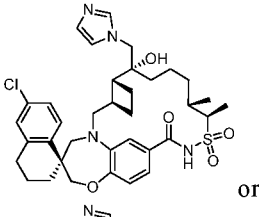
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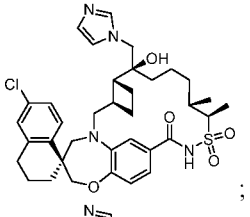
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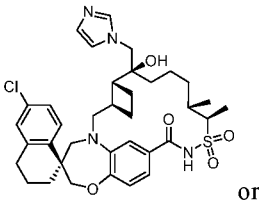
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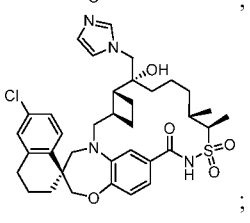
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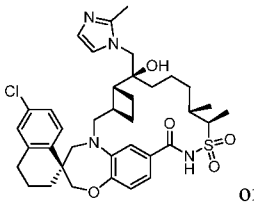
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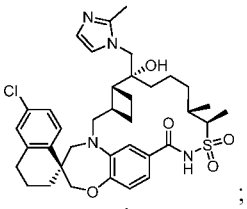
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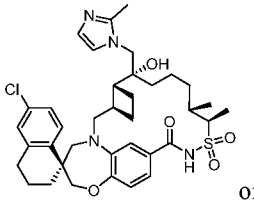
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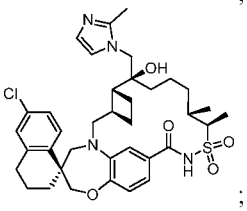
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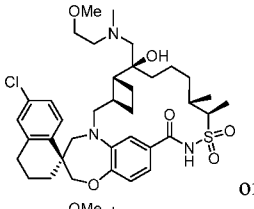
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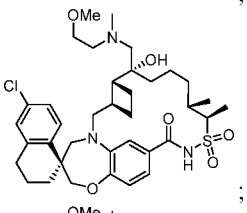
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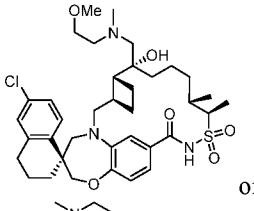
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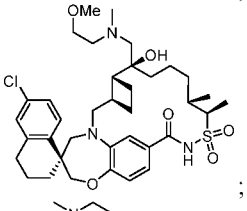
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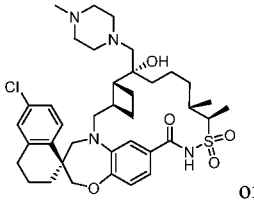
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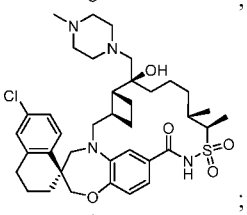
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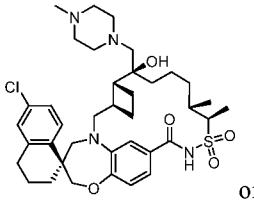
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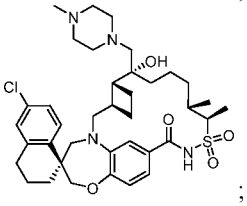
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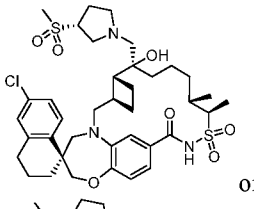
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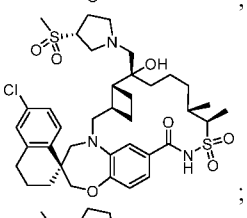
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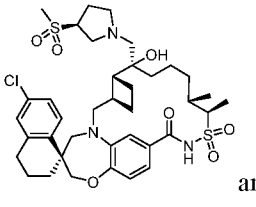
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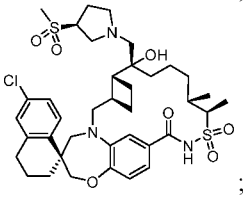
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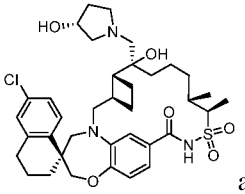
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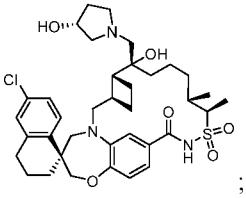
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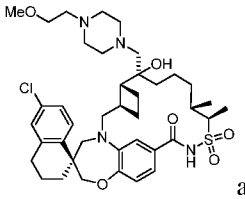
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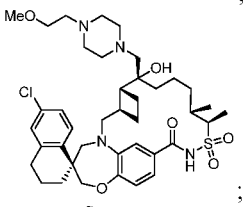
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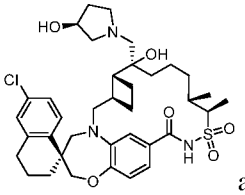
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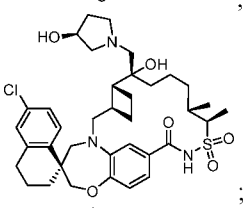
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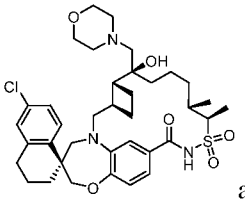
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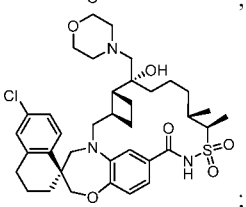
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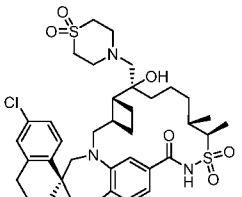
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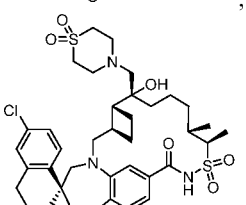
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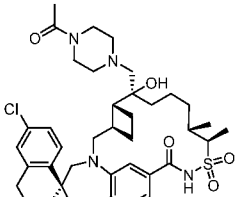
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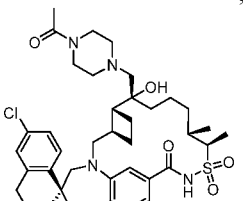
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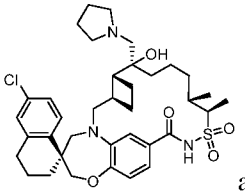
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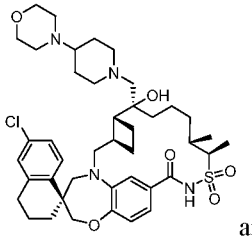
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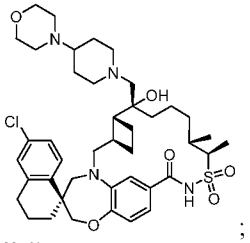
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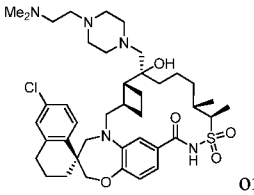
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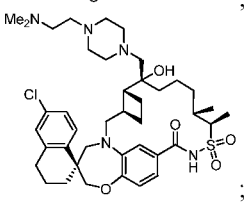
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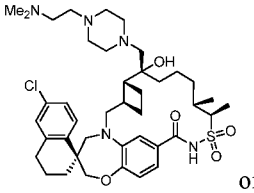
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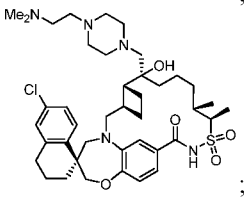
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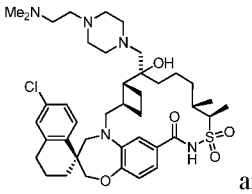
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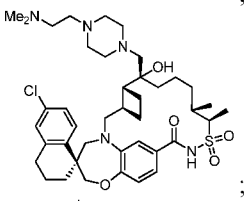
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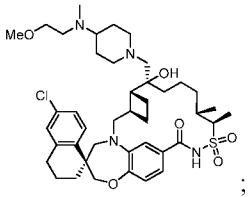
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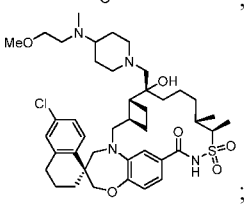
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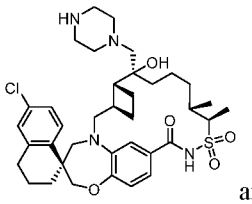
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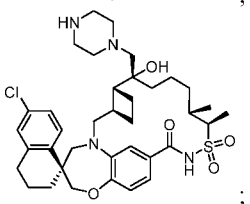
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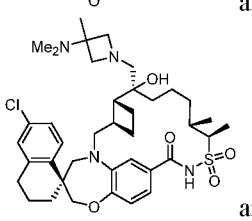
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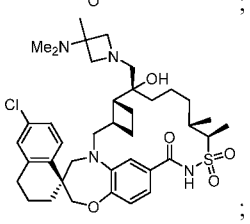
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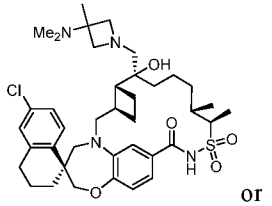
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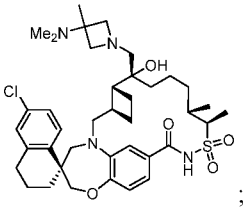
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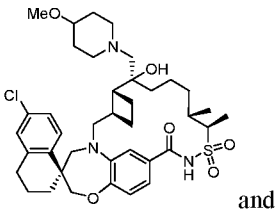
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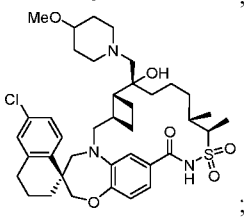
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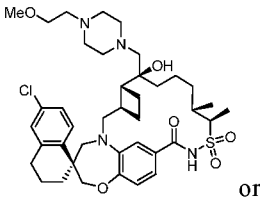
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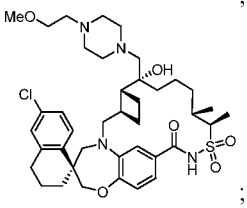
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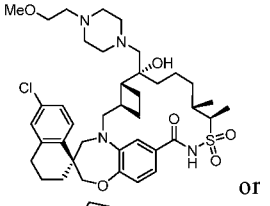
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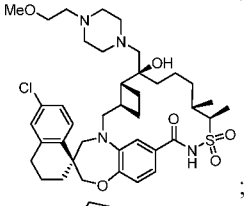
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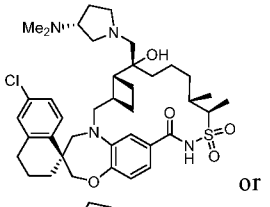
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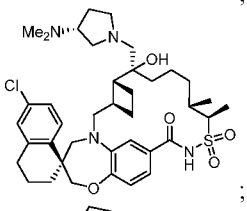
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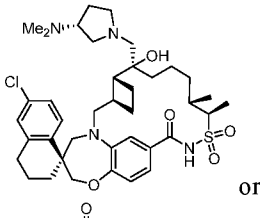
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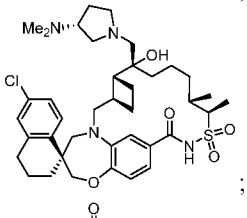
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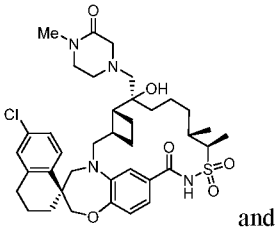
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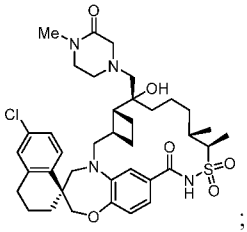
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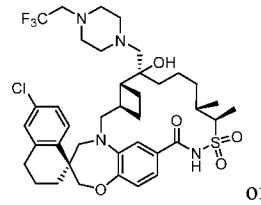
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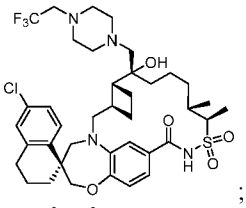
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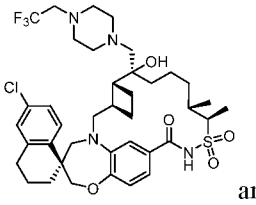
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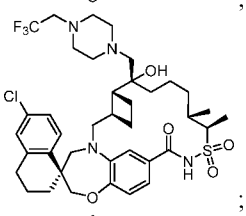
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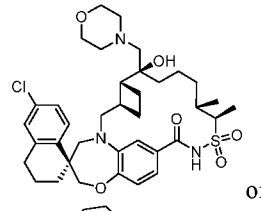
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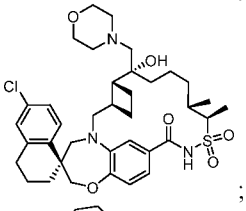
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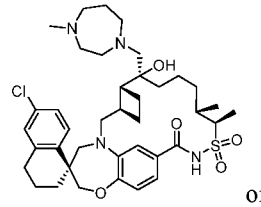
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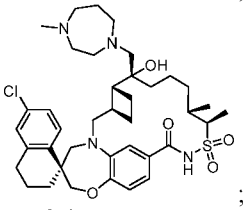
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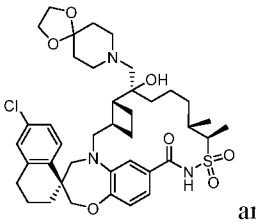
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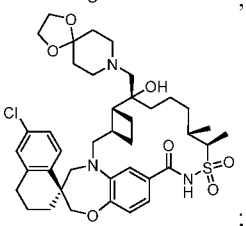
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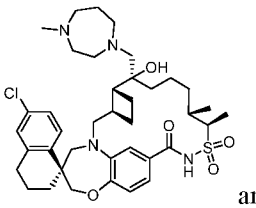
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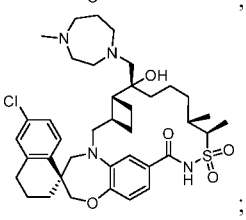
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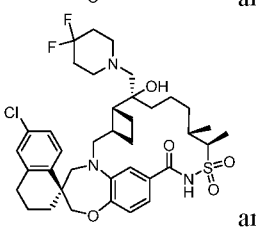
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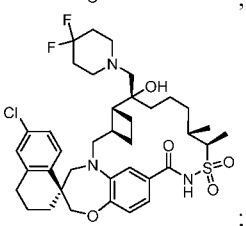
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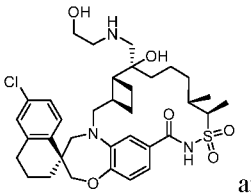
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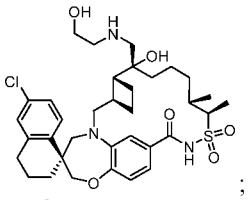
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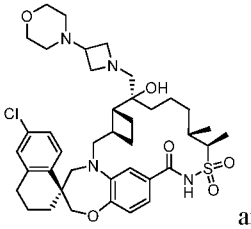
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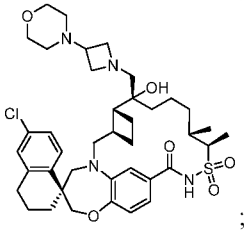
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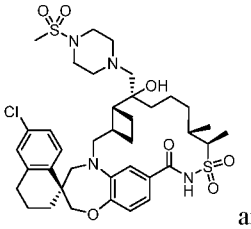
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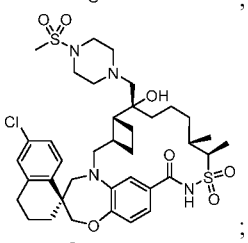
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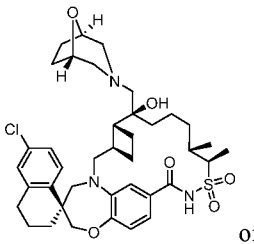
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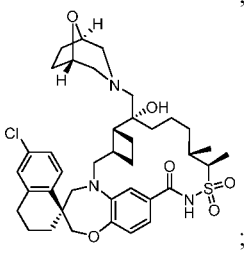
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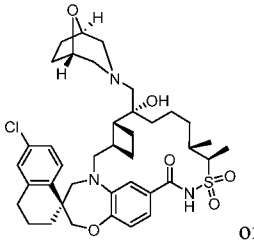
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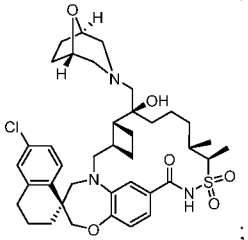
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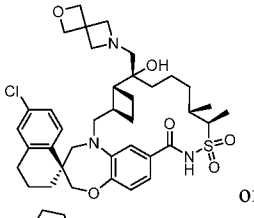
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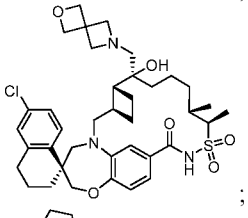
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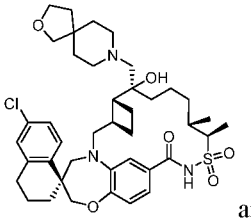
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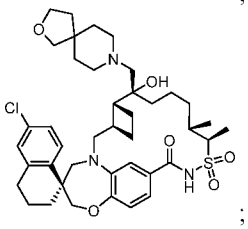
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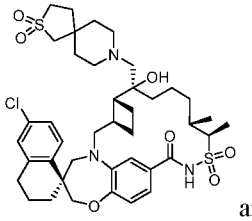
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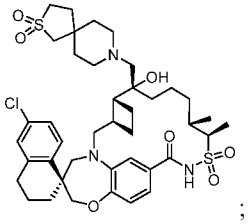
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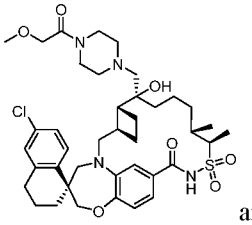
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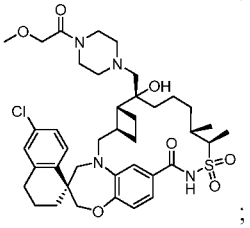
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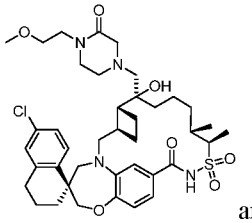
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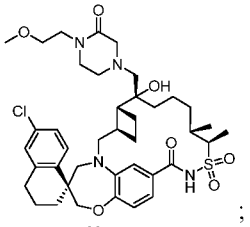
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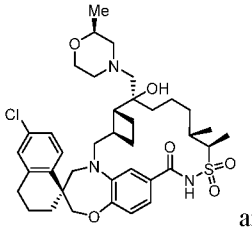
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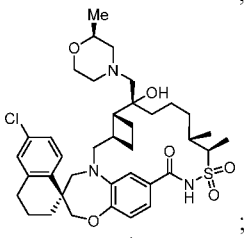
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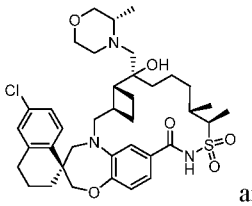
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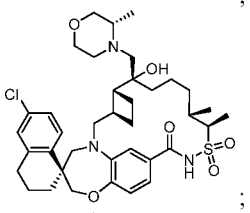
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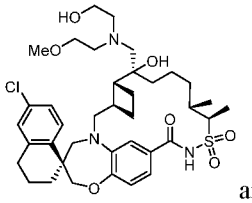
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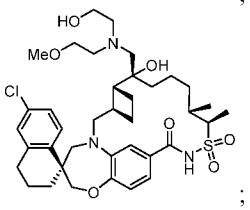
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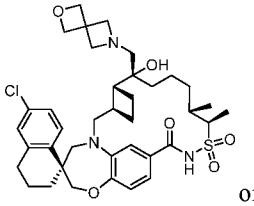
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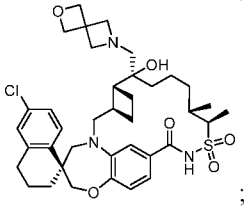
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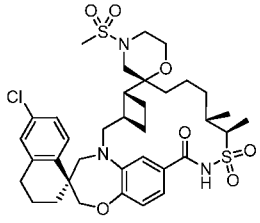
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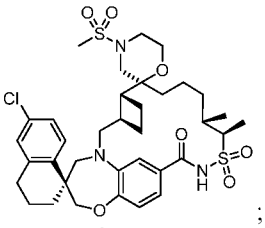
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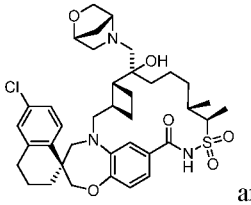
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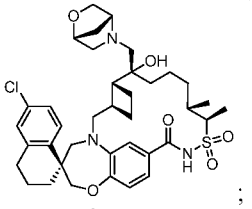
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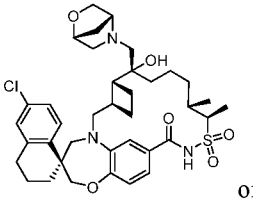
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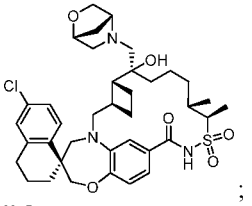
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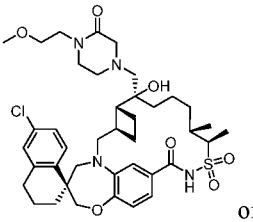
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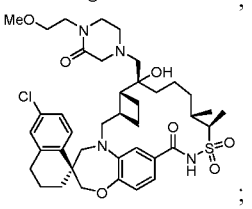
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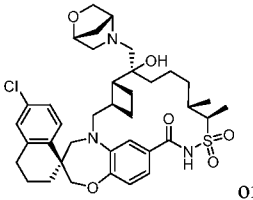
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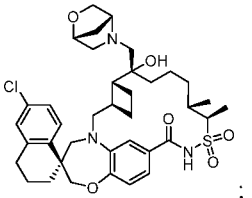
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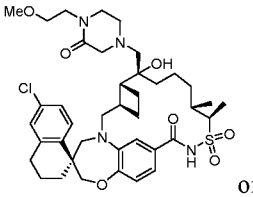
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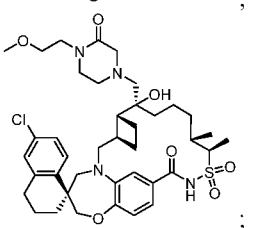
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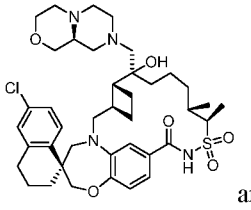
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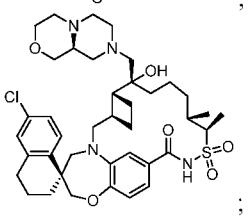
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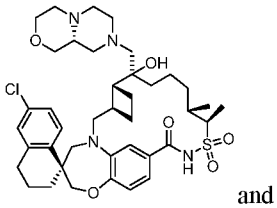
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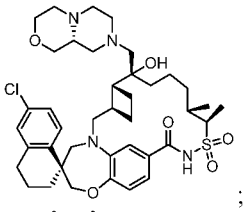
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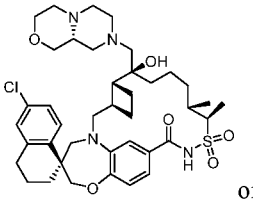
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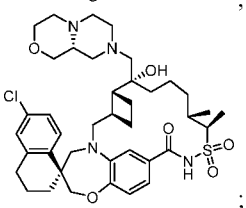
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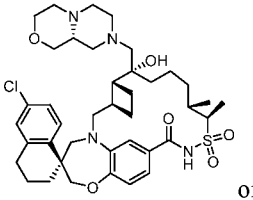
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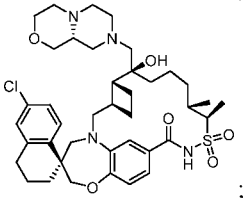
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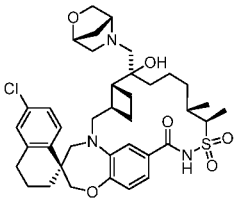
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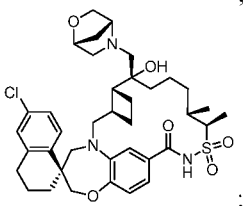
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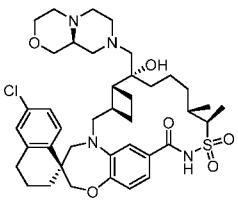
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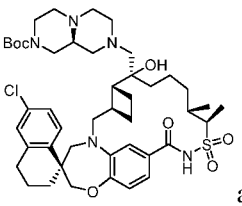
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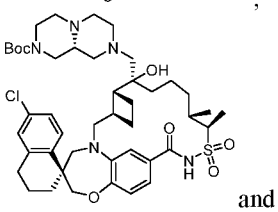
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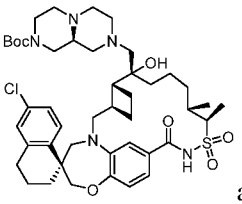
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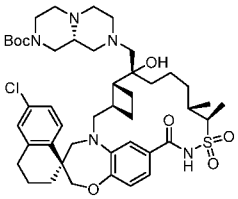
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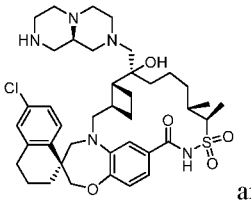
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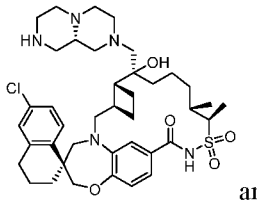
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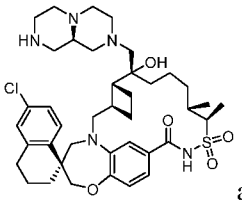
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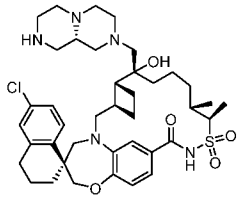
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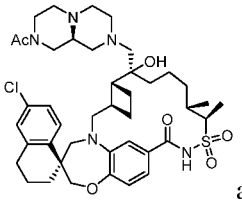
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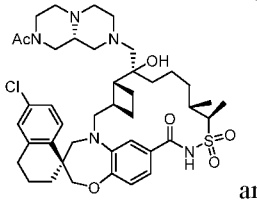
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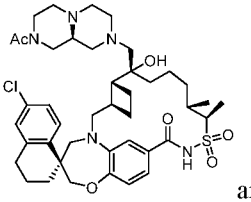
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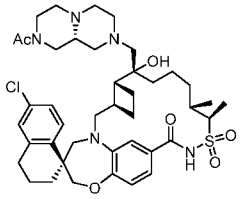
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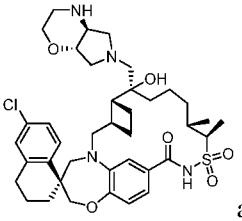
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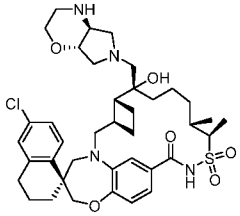
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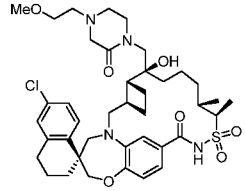
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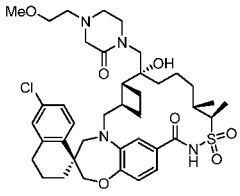
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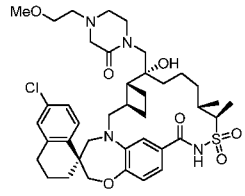
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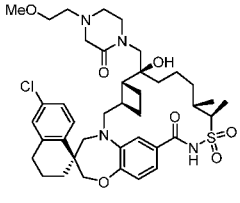
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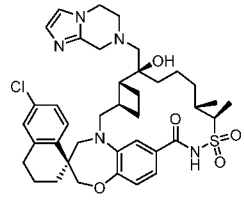
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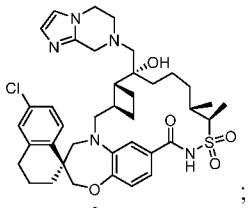
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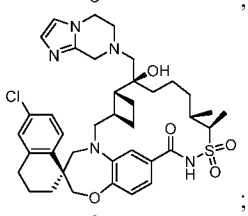
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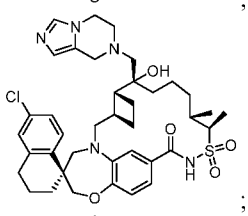
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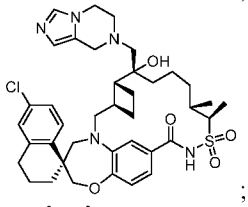
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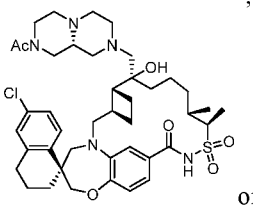
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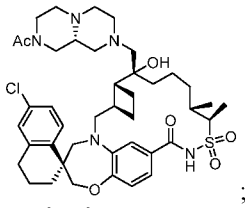
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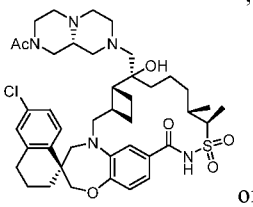
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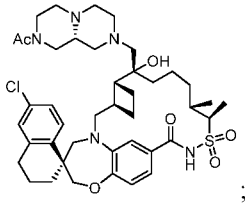
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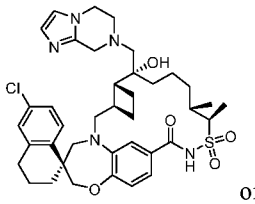
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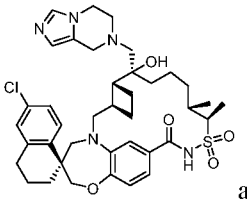
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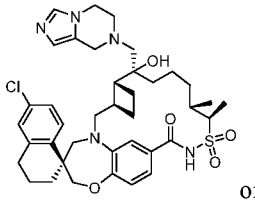
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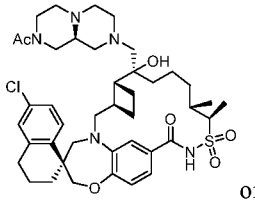
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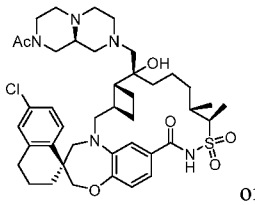
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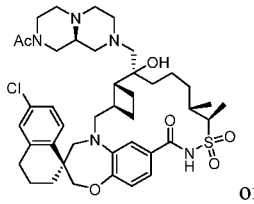
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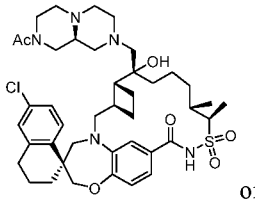
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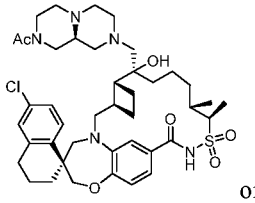
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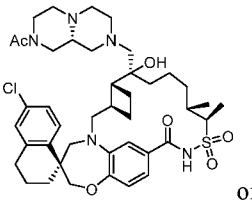
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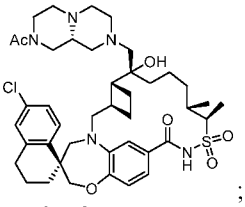
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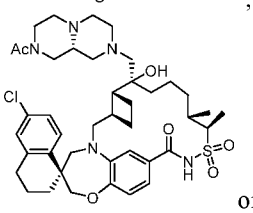
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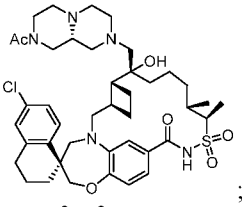
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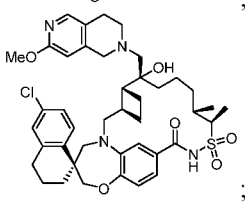
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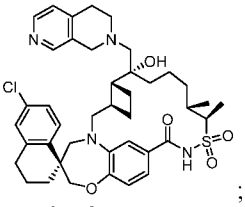
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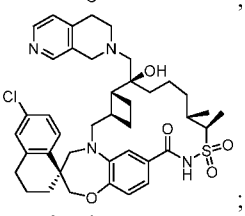
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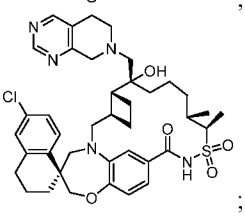
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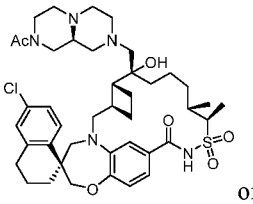
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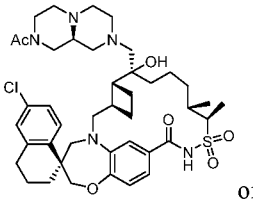
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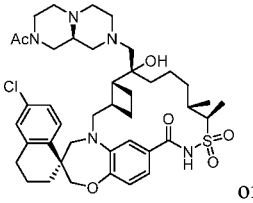
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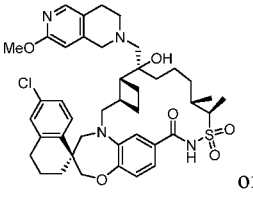
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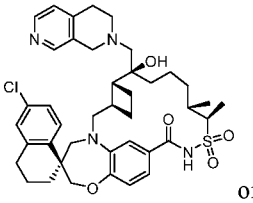
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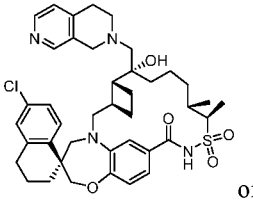
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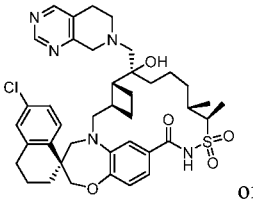
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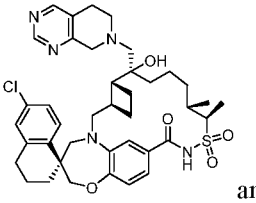
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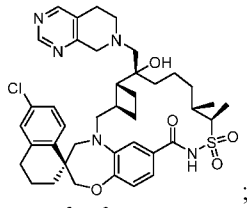
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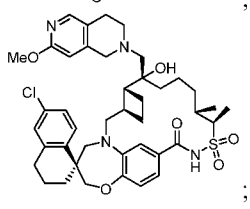
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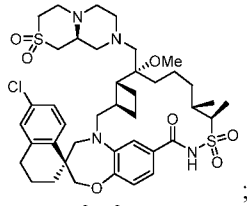
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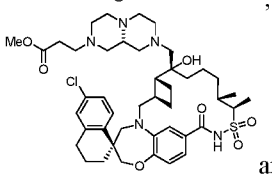
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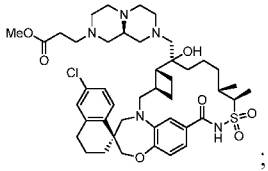
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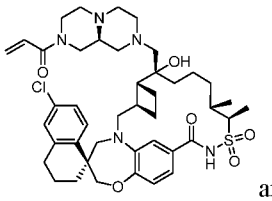
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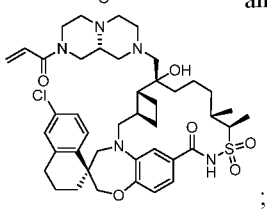
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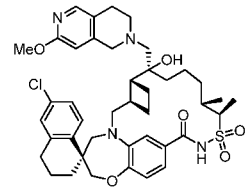
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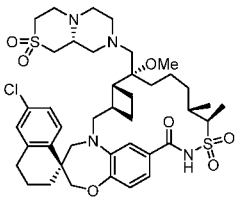
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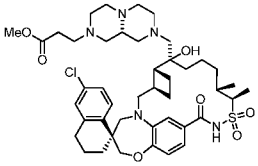
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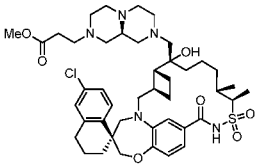
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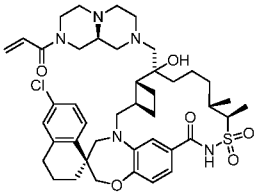
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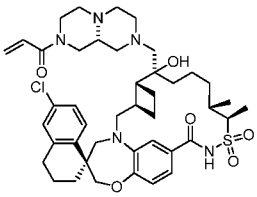
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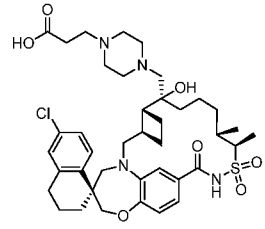
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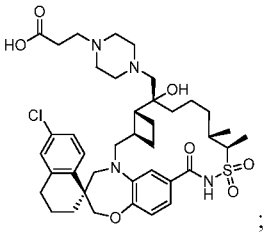
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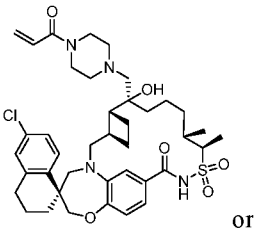
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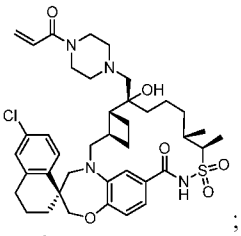
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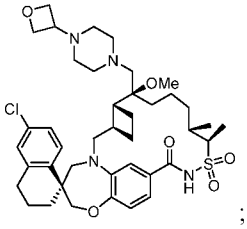
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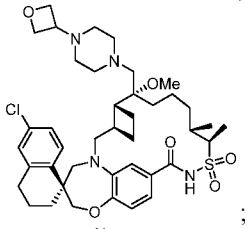
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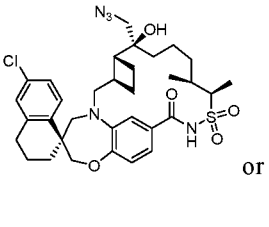
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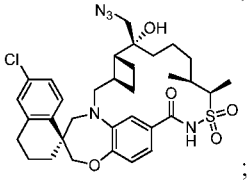
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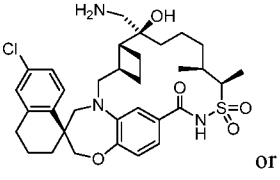
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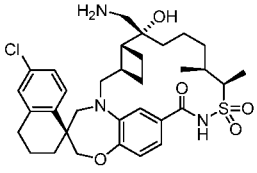
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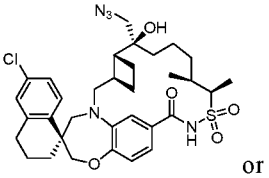
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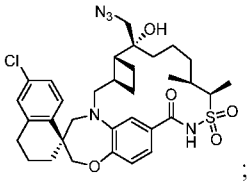
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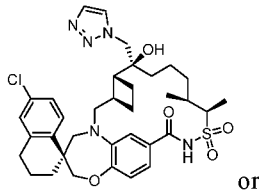
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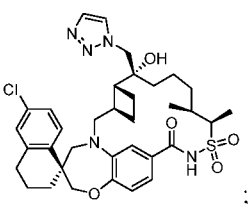
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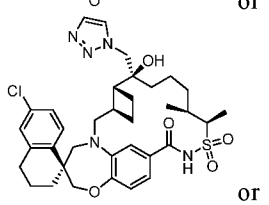
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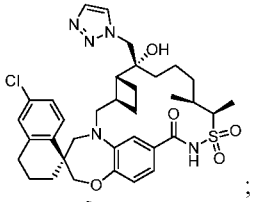
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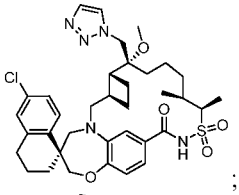
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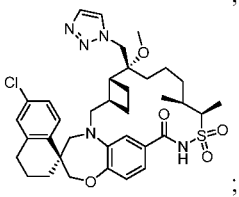
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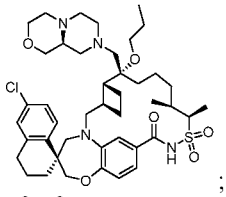
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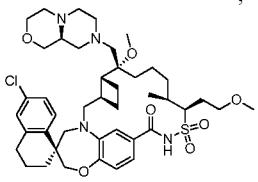
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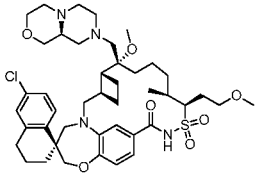
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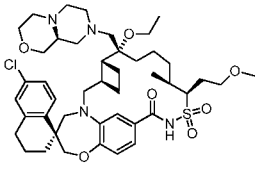
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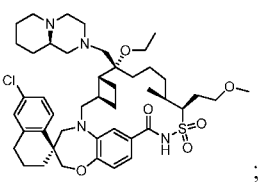
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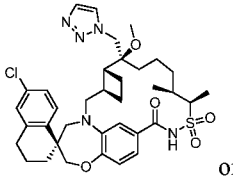
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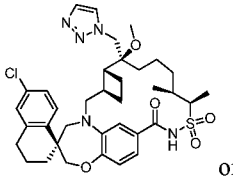
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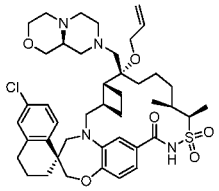
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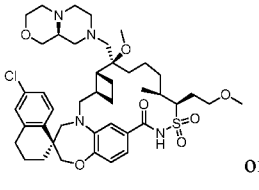
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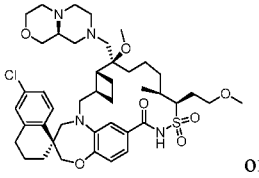
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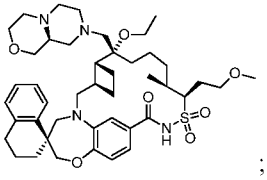
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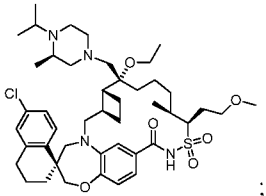
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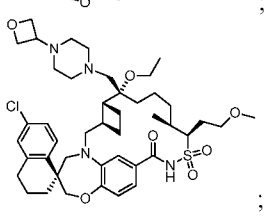
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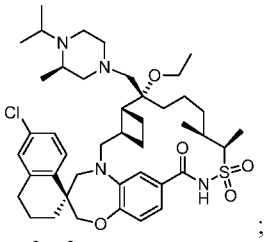
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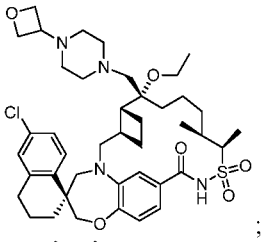
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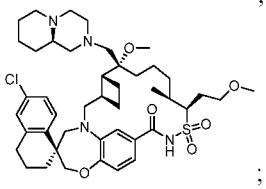
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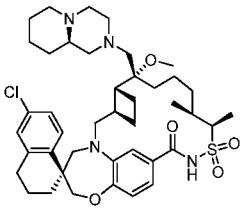
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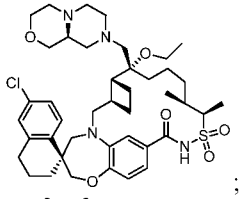
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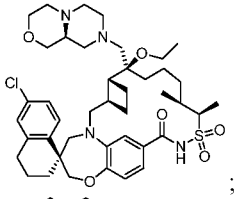
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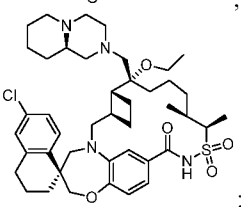
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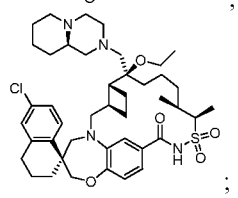
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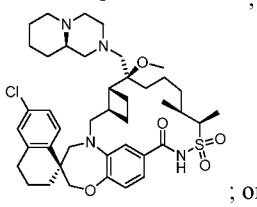
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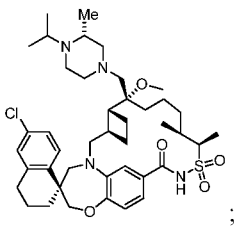
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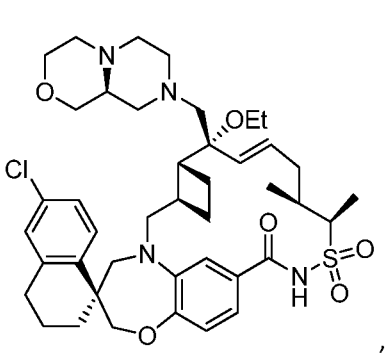
or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof.

145. The compound of embodiment 144 or the pharmaceutically acceptable salt thereof.

146. Another embodiment of the present invention comprises the compound of Embodiment 1, wherein the compound is selected from: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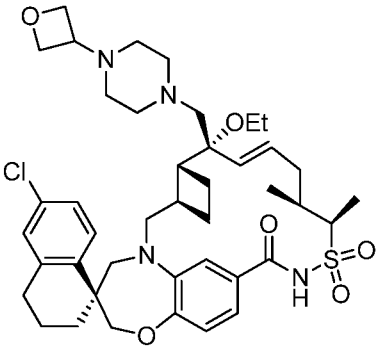
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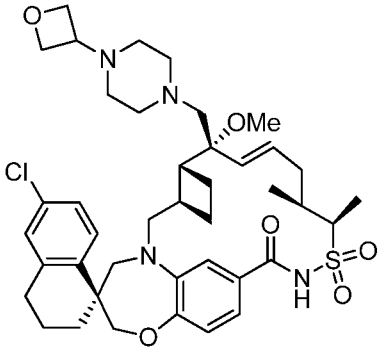
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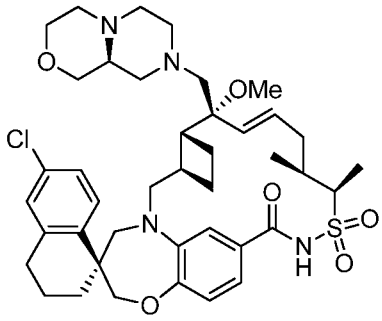
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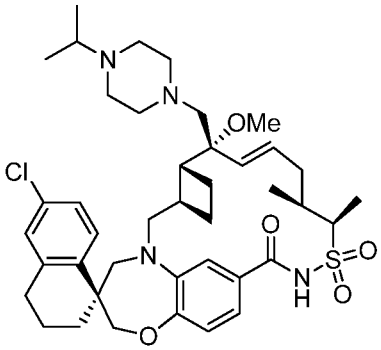
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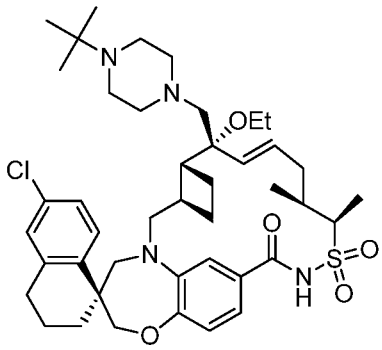
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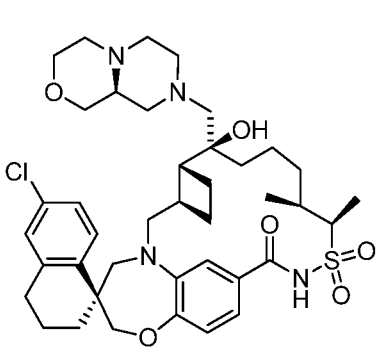
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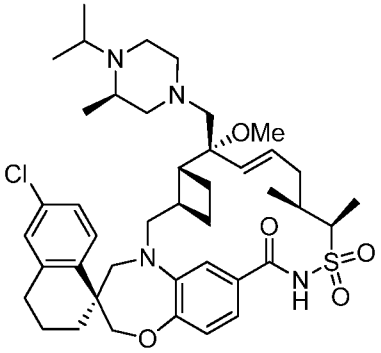
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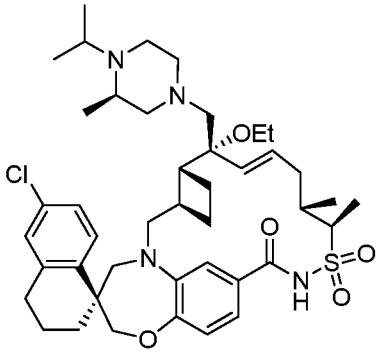
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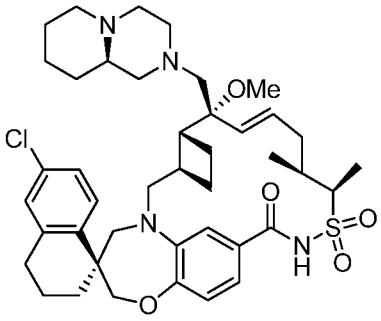
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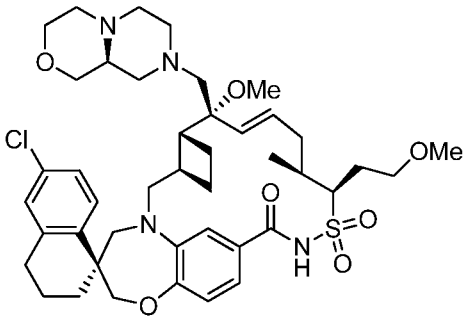
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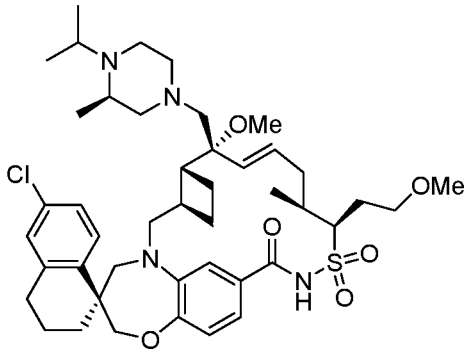
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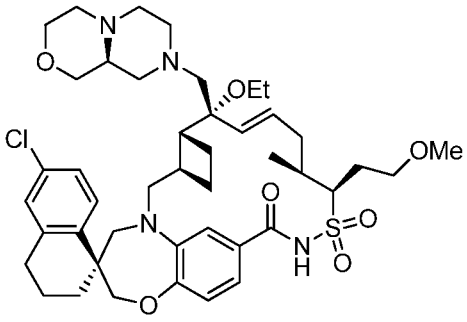
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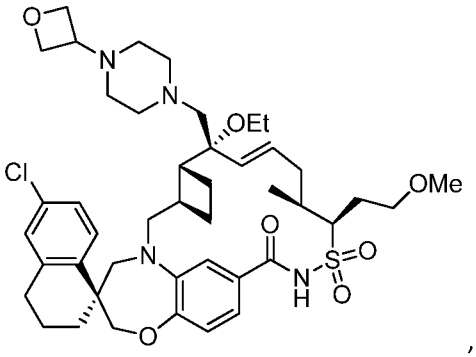
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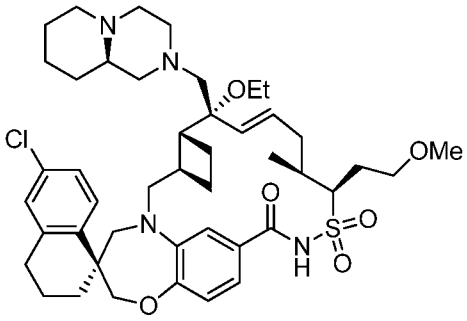
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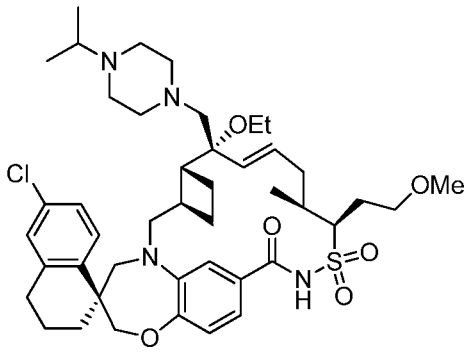
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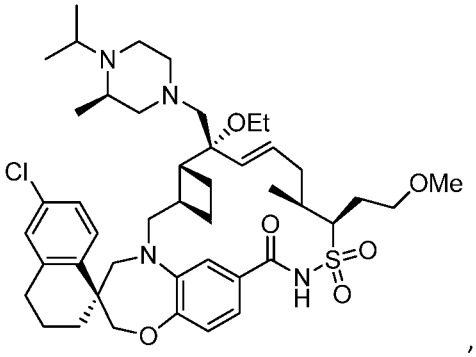
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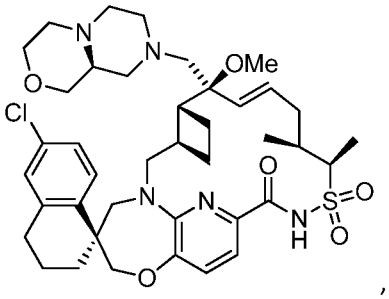
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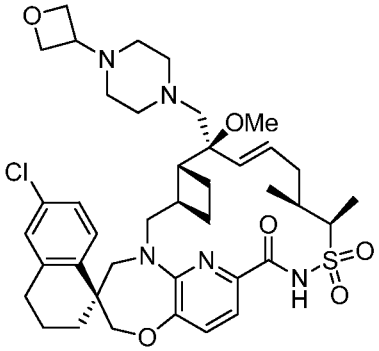
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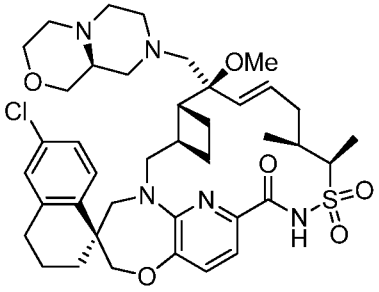
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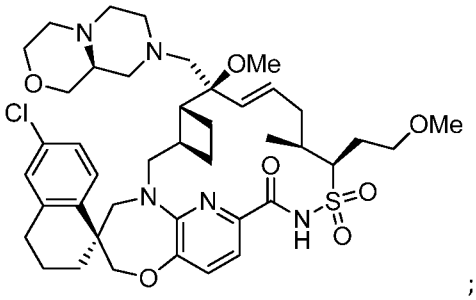

;

or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof.

147. The compound of embodiment 146 or the pharmaceutically acceptable salt thereof.

148. Another embodiment of the present invention comprises a pharmaceutical composition comprising the compound of any one of Embodiments 1-147 or the pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

149. Another embodiment of the present invention comprises a method of treating cancer, the method comprising: administering to a patient in need thereof a therapeutically effective amount of the compound of any of Embodiments 1-147 or the pharmaceutically acceptable salt thereof.

150. The method of Embodiment 149, wherein the cancer is a hematologic malignancy.

151. The method of Embodiment 149, wherein the cancer is selected from the group consisting of breast cancer, colorectal cancer, skin cancer, melanoma, ovarian cancer, kidney cancer, lung cancer, non-small cell lung cancer, lymphoma, non-Hodgkin's lymphoma, myeloma, multiple myeloma, leukemia, and acute myelogenous leukemia.

152. The method of Embodiment 149, wherein the cancer is multiple myeloma.

153. The method of Embodiment 149, further comprising administering to the patient in need thereof a therapeutically effective amount of an additional pharmaceutically active compound.

154. The method of Embodiment 153, wherein the additional pharmaceutically active compound is carfilzomib.

155. The method of Embodiment 153, wherein the additional pharmaceutically active compound is venetoclax.

156. The method of Embodiment 153, wherein the additional pharmaceutically active compound is cytarabine.

157. Another embodiment of the present invention comprises the use of a compound according to any one of Embodiments 1-147 for treating cancer in a subject.

158. Another embodiment of the present invention comprises the compound according to any one of Embodiments 1-147 in the preparation of a medicament for treating cancer.

159. The compound according to Embodiment 158, wherein the cancer is a hematologic malignancy.

160. The compound according to Embodiment 158, wherein the cancer is selected from the group consisting of breast cancer, colorectal cancer, skin cancer, melanoma, ovarian cancer, kidney cancer, lung cancer, non-small cell lung cancer, lymphoma, non-Hodgkin's lymphoma, myeloma, multiple myeloma, leukemia, and acute myelogenous leukemia.

161. The compound according to Embodiment 158, wherein the cancer is multiple myeloma.

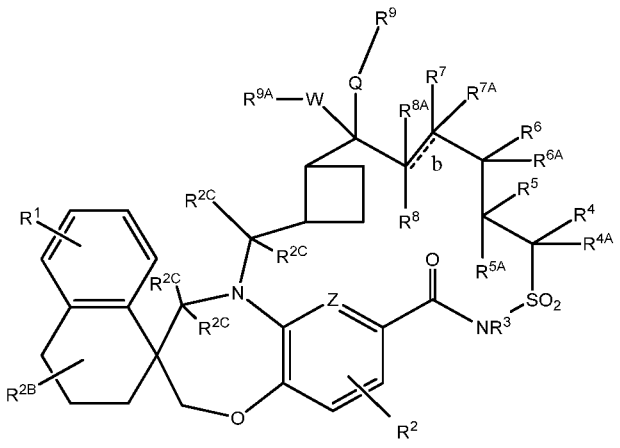
162. The compound according to Embodiment 158, wherein the cancer is acute myelogenous leukemia.

163. The compound according to Embodiment 158, wherein the cancer is non-Hodgkin's lymphoma.

EMBODIMENTS B

The embodiments listed below are presented in numbered form for convenience and for ease and clarity of reference in referring back to multiple embodiments.

In a first embodiment, the present invention comprises a compound of Formula I:



(I);

a stereoisomer thereof, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of the stereoisomer thereof,

wherein:

Z is C or N;

Q is O, S, $CR^{WA}R^{WB}$, or NR^aR^b;

W is $CR^{WA}R^{WB}$, -C=O, or is absent;

R^{WA} and R^{WB} are independently selected from H, -C_{1-3}alkyl, -C_{2-3}alkenyl, -C_{2-3}alkynyl, halo, -OH, or -O-C_{1-3}alkyl;

b, represented by the symbol ------, is a single or double chemical bond which may be cis or trans;

R^1 is independently selected from H, halo, C_{1-6}alkylhalo, C_{1-6}alkyl, C_{2-6}alkenyl, -$(CH_2CH_2O)_nR^a$, -SO_2R^a, -C(=O)R^a ,-C(=O)OR^a, or -C(=O)NR^aR^b;

R^2 is selected from H, halo, C_{1-6}haloalkyl, C_{1-6}alkyl, O-C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkenylene, -C_{1-6}alkyl-O-C_{1-6}alkyl, -$(CH_2CH_2O)_nR^a$, -SO_2R^a, -C(=O)R^a , -C(=O)OR^a, -OC(=O)R^a, -C(=O)NR^aR^b, a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, or a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl or heterocycloalkyl group have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups

may include a C=O group , and further wherein the spiroheterocycloalkyl, and heterocycloalkyl groups may include a S=O or SO_2;

R^3 is selected from H, -C_{1-6}alkylhalo, -C_{1-6}alkyl, -C_{2-6}alkenyl, -$(CH_2CH_2O)_nR^a$, -C(=O)R^a, -C(=O)OR^a, or -C(=O)NR^aR^b;

each of R^{2B}, R^{2C}, R^4, R^5, R^6, R^7, and R^8 is independently selected from H, halo, -C_{1-6}haloalkyl, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{1-6}alkyl-O-C_{1-6}alkyl, -$(CH_2CH_2O)_nR^a$, -SO_2R^a, -C(=O)R^a ,-C(=O)OR^a, -OC(=O)R^a, -C(=O)NR^aR^b, a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl and heterocycloalkyl groups have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group , and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2;

alternatively R^3 and R^4 together with the atoms to which they are bonded may form a 5- to 12-membered ring, optionally containing a heteroatom selected from a N, O or S atom, in addition to the S and N atoms present in the ring, wherein the ring may optionally contain at least one double bond; and the ring may be substituted with 0, 1, 2, or 3 R^{3A} substituents;

wherein R^{3A} is selected from H, halo, -OH, C_{1-6}haloalkyl, C_{1-6}alkyl, O-C_{1-6}alkyl, C_{2-6}alkenyl, -C_{1-6}alkyl-O-C_{1-6}alkyl, -$(CH_2CH_2O)_nR^a$, -SO_2R^a, -C(=O)R^a ,-C(=O)OR^a, -OC(=O)R^a, or -C(=O)NR^aR^b;

each of R^{4A}, R^{5A}, R^{6A}, R^{7A}, and R^{8A} is independently selected from H, OH, halo, or -C_{1-6}alkyl;

R^{7A} and R^{8A} are absent when b is a double chemical bond;

alternatively R^7 and R^8 together with the atoms to which they are bonded may form a 3- to 12-membered ring, wherein the ring may optionally contain at least one double bond;

R^9 is independently selected from H, OH, -(=O), -C_{1-6}haloalkyl, -C_{1-6}alkyl, -C_{1-6}alkenylene, -$(CH_2CH_2O)_nR^a$, -C(=O)R^a ,-C(=O)OR^a, -C(=O)NR^aR^b, -C_{1-}

$_{6}$alkyl-O-C_{1-6}alkyl, cyano, a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl or heterocycloalkyl groups have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, and the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl group may include a C=O group, and further wherein the spiroheterocycloalkyl, and heterocycloalkyl groups may include a S=O or SO_2;

R^{9A} is independently selected from H, -OH, halo, cyano, -C_{1-6}haloalkyl, -C_{1-6}alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -C_{1-6}alkenylene, -$(CH_2CH_2O)_nR^a$, -$P(=O)OR^aOR^b$, -CSR^a, -$CS(=O)R^a$, -SR^a, -SOR^a, -OSO_2R^a, -SO_2R^a, -$(CH_2CH_2O)_nCH_3$, -(=O), -C(=O), -$C(=O)R^a$, -$C(=O)OR^a$, -$C(=O)NR^aR^b$, -CH_2-NR^aR^b, -NR^aR^b, -C_{1-6}alkyl-O-C_{1-6}alkyl, -OC_{1-6}alkyl, -O-C_{1-6}alkyl-O-C_{1-6}alkyl, phenyl, a 6- to 12-membered aryl, a 6-to 12-membered heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl and heterocycloalkyl groups have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may contain a double bond and may contain a C=O group, and further wherein the spiroheterocycloalkyl, and heterocycloalkyl groups may include a S=O or SO_2;

wherein R^{9A} is not H when W is absent;

wherein the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, spirocycloalkyl and spiroheterocycloalkyl groups of the R^{9A} substituent can be unsubstituted or substituted with 1, 2, 3 or 4 R^{10} substituents independently selected from OH, halo, -NR^cR^d, -C_{1-6}alkyl, -C_2-C_6 alkenyl, -C_2-C_6alkynyl, -OC_{1-6}alkyl, -C_{1-6}alkyl-OH, -C_{1-6}alkyl-O-C_{1-6}alkyl, C_{1-6}haloalkyl, -O-haloC_{1-6}alkyl, -SO_2R^c, -CN, -$C(=O)NR^cR^d$, -$C(=O)R^c$, -$OC(=O)R^a$, -$C(=O)OR^c$, a 6- to 12-membered aryl, a 6- to 12-membered heteroaryl, a 5- to 12-membered spirocycloalkyl or

spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl, and heterocycloalkyl groups have 0, 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group, and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2;

alternatively R^7 and R^{9A} together with the atoms to which they are bonded may form a 3- to 12-membered ring, wherein the ring may optionally contain at least one double bond;

alternatively R^9 and R^{9A} together with Q, W, and the C to which W and Q are bonded, may form a 3- to 12-membered monocyclic or bicyclic ring, optionally containing a heteroatom in addition to Q that is selected from N, O or S, wherein the ring may contain a double bond, wherein the ring may optionally include a C=O group, and further wherein the ring optionally may be substituted by 1, 2, or 3 R^{11} substituents;

R^{11} is independently selected from H, -OH, halo, -C_{1-6}alkyl, -OC_{1-6}alkyl, -C_{1-6}alkyl-OH, -C_{1-6}alkyl-O-C_{1-6}alkyl, -C_{1-6}haloalkyl, -O-haloC_{1-6}alkyl, -SO_2R^c, -CN, -NR^cR^d, -C(=O)NR^cR^d, -C(=O)R^c, -OC(=O)R^c, -C(=O)OR^c , a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl, and heterocycloalkyl groups have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl group may include a double bond, and wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl group may include a C=O group, and further wherein the spiroheterocycloalkyl, and heterocycloalkyl groups may include a S=O or SO_2;

wherein the C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl and the -OC_{1-6}alkyl of any of the R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{4A}, R^{5A}, R^{6A}, R^{7A}, R^{8A}, R^{9A},

R^{WA} and R^{WB} substituents is unsubstituted or substituted by 1, 2 or 3 R^{12} substituents independently selected from OH, -OC_{1-6}alkyl, -C_{1-6}alkyl-O-C_{1-6}alkyl, halo, -O-haloC_{1-6}alkyl, -CN, -NR^aR^b, -$(NR^aR^bR^c)_n$, -OSO_2R^a, -SO_2R^a, -$(CH_2CH_2O)_nCH_3$, -(=O), -C(=O), -$C(=O)R^a$, -$OC(=O)R^a$, -$C(=O)OR^a$, -$C(=O)NR^aR^b$, -O-$SiR^aR^bR^c$, -$SiR^aR^bR^c$, -O-(3- to 10-membered heterocycloakyl), a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl and heterocycloalkyl groups have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, and heterocycloalkyl groups may include a C=O group, and further wherein the spiroheterocycloalkyl, and heterocycloalkyl groups may include a S=O or SO_2;

wherein the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, spirocycloalkyl and spiroheterocycloalkyl group of any of the R^2, R^4, R^5, R^6, R^7, R^8, R^9, R^{9A}, R^{10}, R^{11}, R^{12}, R^{WA} and R^{WB} substituents can be unsubstituted or substituted with 1, 2, 3 or 4 R^{13} substituents independently selected from OH, halo, -NR^cR^d, -C_{1-6}alkyl, -OC_{1-6}alkyl, - C_{1-6}alkyl-OH, -C_{1-6}alkyl-O-C_{1-6}alkyl, C_{1-6}haloalkyl, -O-haloC_{1-6}alkyl, -SO_2R^c, -CN, -$C(=O)NR^cR^d$, -$C(=O)R^c$, -$OC(=O)R^a$, -$C(=O)OR^c$, a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, spiroheterocycloalkyl, and heterocycloalkyl groups of R^{13} have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl, spirocycloalkyl, and spiroheterocycloalkyl groups of R^{13} or the heterocycloalkyl group of R^{13} may include a C=O group , and further wherein the spiroheterocycloalkyl and heterocycloalkyl groups may include a S=O or SO_2;

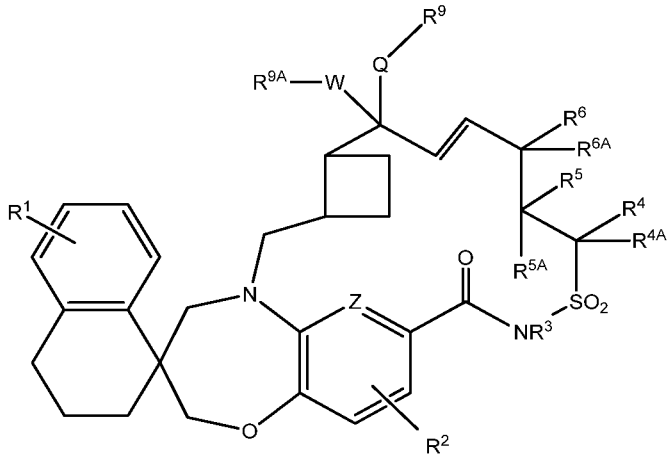
wherein each R^a, R^b, R^c, and R^d is independently hydrogen, OH, -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{1-6}alkyl-$NR^{14}R^{14}$, -$NR^{14}R^{14}$, -SO_2R^{14}, -$(CH_2CH_2O)_nCH_3$, -(=O), -$C(=O)R^{14}$, -$OC(=O)R^{14}$, -$C(=O)OR^{14}$, -$C(=O)NR^{14}R^{14}$,

-C_{1-6}haloalkyl, -O-haloC_{1-6}alkyl, -C_{1-6}alkyl-O-C_{1-6}alkyl, benzyl, phenyl, -C_{1-6}alkyl–C(=O)OH, -C_{1-6}alkyl–C(=O)-O-C_{1-6}alkyl, -C_{1-6}alkyl–cycloalkyl, -C_{1-6}alkyl–heterocycloalkyl, -C_{1-6}alkyl– 6- to 10-membered aryl, -C_{1-6}alkyl–6- to 10-membered heteroaryl, a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, or a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, where the heteroaryl, spiroheterocycloalkyl, heterocycloalkyl group or the -C_{1-6}alkyl–heterocycloalkyl groups have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, and the cycloalkyl, spirocycloalkyl, spiroheterocycloalkyl, heterocycloalkyl, group of R^a, R^b, R^c, and R^d or the heterocycloalkyl group or the -C_{1-6}alkyl–heterocycloalkyl group may include a double bond and may contain a C=O group, and the spiroheterocycloalkyl, or heterocycloalkyl may include a S=O or SO_2;

the alkyl, aryl, heteroaryl, spirocycloalkyl, spiroheterocycloalkyl, cycloalkyl, or heterocycloalkyl group of R^a, R^b, R^c, and R^d and the heterocycloalkyl group of the -C_{1-6}alkyl–heterocycloalkyl group of R^a, R^b, R^c, and R^d can be unsubstituted or substituted with 1, 2, 3, or 4 R^{14} substituents, wherein each R^{14} is independently selected from H, -OH, -N=N=N, halo, -C_{1-6}alkyl, -C_{1-6}haloalkyl, -OC_{1-6}alkyl, -C_{1-6}alkyl-O-C_{1-6}alkyl, -C_{1-6}haloalkyl, -O-haloC_{1-6}alkyl, phenyl, tolyl, -C(=O)C_{1-6}alkyl, -C(=O)O-C_{1-6}alkyl, $N(CH_3)_2$ or -SO_2-$N(CH_3)_2$; and

wherein n is independently in each instance an integer of 1, 2, 3 or 4.

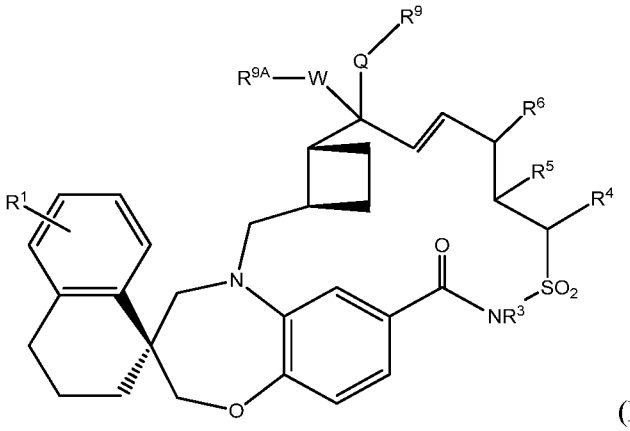
2. Another embodiment of the present invention comprises the compound of embodiment 1, wherein the compound has the Formula II:



(II);

or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof.

3. Another embodiment of the present invention comprises a compound of any of embodiments 1 or 2, wherein the compound has the Formula IIa:



(IIa);

or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof.

4. The compound of any one of embodiments 1-3, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein Q is O, NR^aNR^b, or S.

5. The compound of any one of embodiments 1-4, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein Q is O.

6. The compound of any one of embodiments 1-5, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein W is $CR^{WA}R^{WB}$, -C=O, or is absent.

7. The compound of embodiment 5, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein W is $CR^{WA}R^{WB}$.

8. The compound of embodiment 5, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein W is absent.

9. The compound of any one of embodiments 1-7, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{WA} and R^{WB} are independently selected from H, (=O), -C_{1-3}alkyl, -C_{2-3}alkenyl, -C_{2-3}alkynyl, halo, -OH, or -O-C_{1-3}alkyl.

10. The compound of embodiment 9, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{WA} and R^{WB} are both H.

11. The compound of embodiment 9, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{WA} is $-CH_3$.

12. The compound of embodiment 9, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{WB} is $-CH_3$.

13. The compound of embodiment 9, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{WA} is –OH and R^{WB} is H.

14. The compound of any one of embodiments 1-13, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^1 is halo.

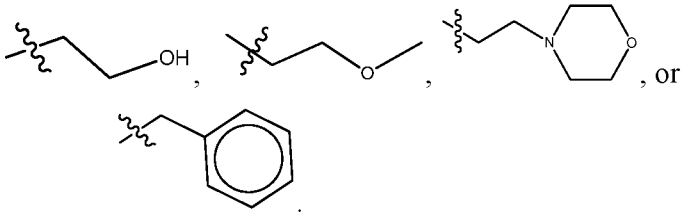
15. The compound of embodiment 14, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^1 is Cl.

16. The compound of any one of embodiments 1-15, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^3 is selected from H and -C_{1-6}alkyl.

17. The compound of embodiment 16, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^3 is H.

18. The compound of any one of embodiments 1-17, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^4 is independently selected from H, -C_{1-6}alkyl, -C_{1-6}alkyl-O-C_{1-6}alkyl, -C_{1-6}alkyl-OH, -C_{1-6}alkyl-OSO_2CH_3, -C_{1-6}alkyl-phenyl, or -C_{1-6}alkyl-(5-6 membered heterocycloalkyl, having one or two heteroatoms independently selected from N or O).

19. The compound of any one of embodiments 1-18, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^4 is independently selected from H, -CH_3, -CH_2CH_3,



, or

20. The compound of embodiment 19, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^4 is –CH_3.

21. The compound of any one of embodiments 1-20, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically

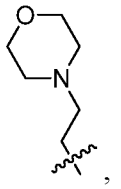
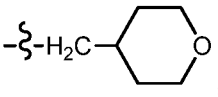
acceptable salt of the stereoisomer thereof, wherein R^5 is selected from H or -C_{1-6}alkyl.

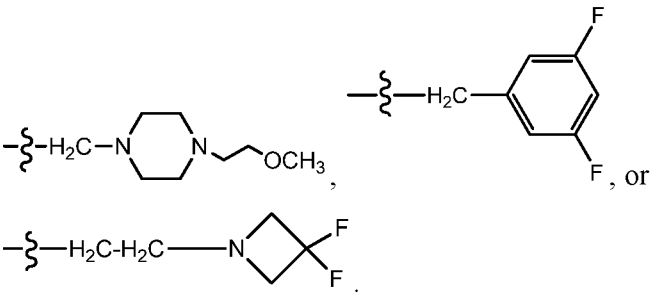
22. The compound of embodiment 21, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^5 is $-CH_3$.

23. The compound of any one of embodiments 1-22, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^6 is selected from H or -C_{1-6}alkyl.

24. The compound of embodiment 23, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^6 is H.

25. The compound of any one of embodiments 1-24, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^9 is independently selected from H, -C_{1-6}alkyl, -C_{1-6}haloalkyl, -C_{1-6}alkyl-O-C_{1-6}alkyl, -C_{1-6}alkyl-(5-6 membered heterocycloalkyl), wherein the heterocycloalkyl has one or two heteroatoms independently selected from N or O, or -C_{1-6}alkyl-phenyl, wherein the phenyl of the -C_{1-6}alkyl-phenyl of the R^9 groups is unsubstituted or substituted with 1 or 2 R^{13} substituents selected from halo or -C_{1-6}alkyl-O-C_{1-6}alkyl.

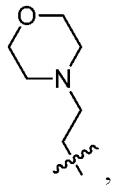
26. The compound of embodiment 25, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^9 is independently selected from H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $CH_2CH_2OCH_3$, CH_2CF_3,  ,  ,



27. The compound of embodiment 26, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^9 is H.

28. The compound of embodiment 26, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^9 is -C_{1-6}alkyl.

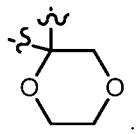
29. The compound of embodiment 26, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^9 is $-CH_3$.

30. The compound of embodiment 26, wherein R^9 is  ,

or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof.

31. The compound of any one of embodiments 1-24, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein alternatively R^9 and R^{9A} together with Q, W, and the C to which W and Q are bonded, may form a 3- to 12-membered monocyclic or bicyclic ring, optionally containing a heteroatom in addition to Q that is selected from N, O or S, wherein the ring may contain a double bond, wherein the ring may optionally include a C=O group.

32. The compound of embodiment 31, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt

of the stereoisomer thereof, wherein R^9 and R^{9A} together with Q, W and the C to which Q and W are bonded form  .

33. The compound of any one of embodiments 1-30, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is independently selected from H, OH, -C_{1-6}alkyl, -C_2-C_6 alkenyl, -C_{2-6}alkynyl; -OC_{1-6}alkyl, -CH_2-NR^aR^b, -C(=O)NR^aR^b, -(=O), -C(=O), C(=O)OR^a, -C(=O)R^a, cyano, -C_{1-6}haloalkyl, -C_{1-6}alkyl-O-C_{1-6}alkyl, -O-C_{1-6}alkyl-O-C_{1-6}alkyl, -P(=O)OR^aOR^b, -SR^a, -OSO_2R^a, -SOR^a, -SO_2R^a, a 6- to 12-membered aryl or heteroaryl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered unsubstituted monocyclic or bicyclic heterocycloalkyl group, wherein the aryl, heteroaryl, or heterocycloalkyl group can have from 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl and the heterocycloalkyl group may contain a double bond and further wherein the cycloalkyl and the heterocycloalkyl group may contain a C=O group;

wherein the aryl, heteroaryl, cycloalkyl, heterocycloalkyl, group of the R^{9A} substituent can be unsubstituted or substituted with from 1, 2, 3 or 4 R^{10} substituents independently selected from OH, halo, -NR^cR^d, -C_{1-6}alkyl, -C_{1-6}alkyl-OH, -C_{1-6}alkyl-O-C_{1-6}alkyl, cyano, -C(=O)OR^c, a 6- to 10-membered aryl, or -SO_2R^c;

wherein the C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and the -OC_{1-6}alkyl of any of the R^{9A} and R^{10} substituents is unsubstituted or substituted by 1, 2 or 3 R^{12} substituents independently selected from OH, halo, -(=O), -OC_{1-6}alkyl, -C_{1-6}alkyl, -NR^aR^b, -$SiR^aR^bR^c$, a 6- to 12-membered aryl or heteroaryl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl, or heterocycloalkyl groups have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl or heterocycloalkyl groups may include a C=O group, and further wherein the heterocycloalkyl group may include a S=O or SO_2;

wherein the -C_{1-6}alkyl groups of the R^{10} substituents is unsubstituted or substituted by 1, 2 or 3 R^{12} substituents of -OC_{1-6}alkyl;

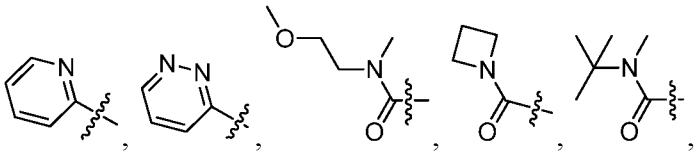
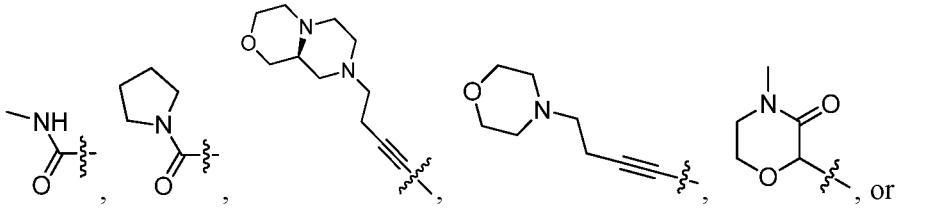
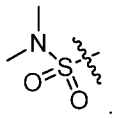
wherein the heterocycloalkyl groups of R^{12} substituents can be unsubstituted or substituted with from 1, 2, 3 or 4 R^{13} substituents independently selected from -NR^cR^d, or -C_{1-6}alkyl;

wherein each R^a, R^b, R^c and R^d is independently hydrogen, OH, -C_{1-6}alkyl, -$(CH_2CH_2O)_nCH_3$, -$NR^{14}R^{14}$, -C_{1-6}alkyl-$NR^{14}R^{14}$, phenyl, -C_{1-6}alkyl–C(=O)OH , -C_{1-6}alkyl–C(=O)-O-C_{1-6}alkyl, -C_{1-6}alkyl–3- to 12-membered cycloalkyl, -C_{1-6}alkyl–3- to 12-membered heterocycloalkyl, -C_{1-6}alkyl–6- to 12-membered heteroaryl, a 6- to 12-membered aryl or heteroaryl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl group, heterocycloalkyl groups of R^a, R^b, R^c, and R^d or the heterocycloalkyl group of the -C_{1-6}alkyl–heterocycloalkyl group of R^a, R^b, R^c, and R^d has from 1, 2, 3, or 4 heteroatoms independently selected from O, N or S, wherein the cycloalkyl and heterocycloalkyl groups of R^a, R^b, R^c, and R^d and the heterocycloalkyl group of the -C_{1-6}alkyl–heterocycloalkyl groups of R^a, R^b, R^c, and R^d may include a double bond, and further wherein the cycloalkyl and heterocycloalkyl groups of R^a, R^b, R^c, and R^d and the heterocycloalkyl group of the -C_{1-6}alkyl–heterocycloalkyl groups of R^a, R^b, R^c, and R^d may contain a C=O group;

the alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl groups of R^a, R^b, R^c, and R^d or the heterocycloalkyl groups of the -C_{1-6}alkyl–heterocycloalkyl groups of R^a, R^b, R^c, and R^d can be unsubstituted or substituted with from 1, 2, 3, or 4 R^{14} substituents,wherein each R^{14} is independently selected from H, OH, halo, -C_{1-6}alkyl, $N(CH_3)_2$, -C_{1-6}haloalkyl, C(=O)CH_3, -C(=O)OCH_3, or -C_{1-6}alkyl-O-C_{1-6}alkyl;

alternatively R^a and R^b together with the atoms to which they are bonded may form a 4- to 12-membered monocyclic or bicyclic ring, optionally containing a heteroatom selected from N, O or S atom, which may contain a double bond; and

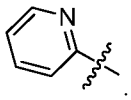
wherein n is independently in each instance an integer from 1, 2, 3 or 4.

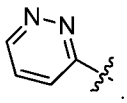
34. The compound of any one of embodiments 1-23, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is independently selected from H, -CH_3, OH,  ,  , or  .

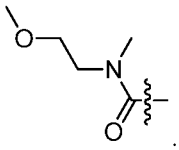
35. The compound of embodiment 34, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is H.

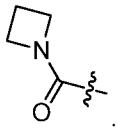
36. The compound of embodiment 34, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is -CH_3.

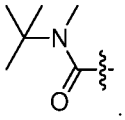
37. The compound of embodiment 34, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is -OH.

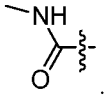
38. The compound of embodiment 34, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is  .

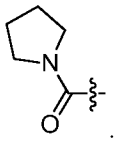
39. The compound of embodiment 34, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is  .

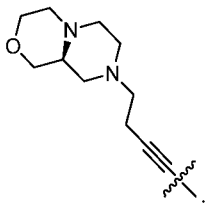
40. The compound of embodiment 34, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is  .

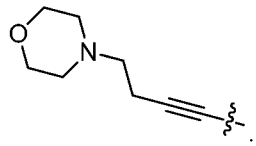
41. The compound of embodiment 34, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is  .

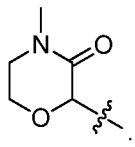
42. The compound of embodiment 34, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is  .

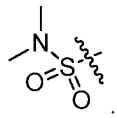
43. The compound of embodiment 34, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is  .

44. The compound of embodiment 34, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is  .

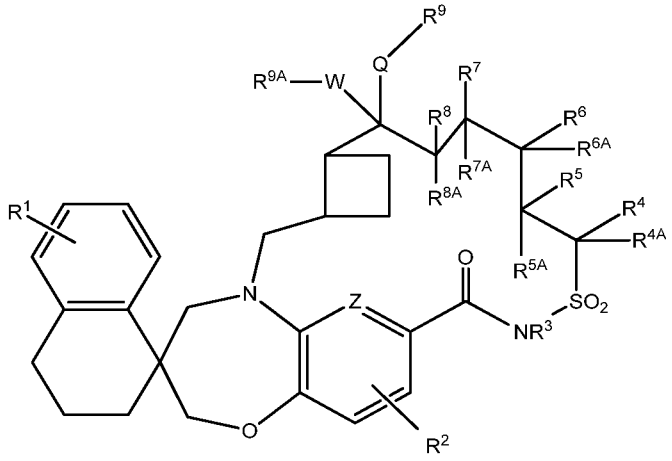
45. The compound of embodiment 34, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is  .

46. The compound of embodiment 34, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is  .

47. The compound of embodiment 34, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is  .

48. The compound of embodiment 34, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is  .

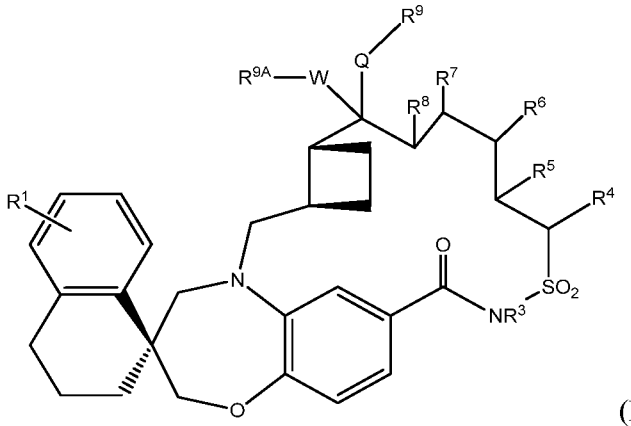
49 Another embodiment of the present invention comprises a compound of embodiment 1, wherein the compound has the Formula III:



(III);

or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof.

50. Another embodiment of the present invention comprises a compound of any one of embodiments 1 or 49, wherein the compound has the Formula IIIa:



(IIIa);

or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof.

51. The compound of any one of embodiments 1, or 49-50, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein Q is O, -CR^aR^b, or -NR^aR^b.

52. The compound of embodiment 51, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein Q is O.

53. The compound of embodiment 52, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein Q is $–CH_2$.

54. The compound of embodiment 52, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein Q is -NR^aR^b.

55. The compound of any one of embodiments 1, or 49-54, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein W is $CR^{WA}R^{WB}$, -C=O, or is absent.

56. The compound of embodiment 55, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein W is $CR^{WA}R^{WB}$.

57. The compound of embodiment 55, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein W is absent.

58. The compound of any one of embodiments 1, or 49-56, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{WA} and R^{WB} are independently selected from H, -C_{1-3}alkyl, -C_{1-3}alkenyl, -C_{1-3}alkynyl, halo, -OH, or -O-C_{1-3}alkyl.

59. The compound of embodiment 58, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{WA} and R^{WB} are both H.

60. The compound of embodiment 58, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{WA} is $-CH_3$.

61. The compound of embodiment 58, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein at least one of R^{WA} and R^{WB} is H.

62. The compound of embodiment 58, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{WA} is –OH and R^{WB} is H.

63. The compound of any one of embodiments 1, or 49-62, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^1 is halo.

64. The compound of embodiment 63, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^1 is Cl.

65. The compound of any one of embodiments 1, or 49-64, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^3 is H.

66. The compound of any one of embodiments 1, or 49-65, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^4 is independently selected from H or -C_{1-6}alkyl.

67. The compound of embodiment 66, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^4 is $-CH_3$.

68. The compound of any one of embodiments 1, or 49-67, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^5 is selected from H or -C_{1-6}alkyl.

69. The compound of embodiment 68, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^5 is $-CH_3$.

70. The compound of any one of embodiments 1, or 49-69, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^6 is H.

71. The compound of any one of embodiments 1, or 49-70, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^7 is selected from H or -NR^aR^b.

72. The compound of embodiment 71, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^7 is H.

73. The compound of any one of embodiments 1, or 49-73, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^8 is selected from H or -C_{1-6}alkyl.

74. The compound of embodiment 73, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^8 is H.

75. The compound of any one of embodiments 1, or 49-70, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein alternatively R^7 and R^8 together with the atoms to which they are bonded may form a 3- to 12-membered ring.

76. The compound of any one of embodiments 1, 49-70, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein alternatively R^7 and R^{9A} together with the atoms to which they are bonded may form a 3- to 12-membered ring, wherein the ring may optionally contain at least one double bond.

77. The compound of any one of embodiments 1, 49-76, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^9 is independently selected from H, -OH, -(=O), -C_{1-6}alkyl, cyano, -C(=O)-C_{1-6}alkyl, -C(=O)-phenyl, -C_{1-6}alkyl-O- C_{1-6}alkyl, -C_{1-6}alkyl-(5-10 membered mono or bicyclic heterocycloalkyl), wherein the heterocycloalkyl may contain one, two, three or four heteroatoms independently selected from N or O.

78. The compound of any one of embodiments 1, or 49-75, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein alternatively R^9 and R^{9A} together with Q, W and the C to which Q and W are bonded, may form a 3- to 12-membered monocyclic or bicyclic ring, optionally containing a heteroatom in addition to Q selected from N, O or S atom, the ring may contain a double bond, the ring may optionally include a C=O group, and the ring optionally may be substituted with 0, 1, 2, or 3 R^{11} substituents;

wherein R^{11} is selected from H, halo, -OH, -C_{1-6}haloalkyl, -C_{1-6}alkyl, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -C(=O)R^c , -C(=O)NR^cR^d, -NR^cR^d, a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, where the heterocycloalkyl groups

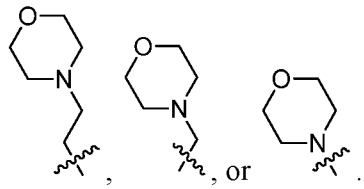
have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, wherein the heterocycloalkyl groups may include a double bond, and wherein the heterocycloalkyl groups may contain a C=O group; and further wherein the heterocycloalkyl groups may be unsubstituted or substituted with one or more -C_{1-6}alkyl.

79. The compound of any one of embodiments 1, 49-75 or 77, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is independently selected from H, -OH, -C_{1-6}alkyl, -C_{2-6} alkenyl, -C_{2-6} alkynyl, -C_{1-6}alkyl, -C(=O), -(=O), -C(=O)Ra, cyano, -C_{1-6}alkyl-O- C_{1-6}alkyl, -O- C_{1-6}alkyl-O-C_{1-6}alkyl, -ORa, -CSRa, -CS(=O)Ra, -SORa, -NRaRb, -C(=O)NRaRb, phenyl, a 6- to 12-membered aryl or heteroaryl, a 5- to 12-membered spirocycloalkyl or spiroheterocycloalkyl, or a 3- to 12-membered cycloalkenyl, a 3- to 12-membered monocyclic or bicyclic cycloalkyl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, wherein the heteroaryl and heterocycloalkyl groups have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, and the cycloalkyl and heterocycloalkyl groups may contain a double bond and wherein the cycloalkyl and heterocycloalkyl groups may contain a C=O group, and further wherein the heterocycloalkyl groups may include a S=O or SO_2;

wherein the aryl, heteroaryl, cycloalkyl, and heterocycloalkyl groups of the R^{9A} substituent can be unsubstituted or substituted with from 1, 2, 3 or 4 R^{10} substituents independently selected from halo, -NR^cR^d, or -C_{1-6}alkyl;

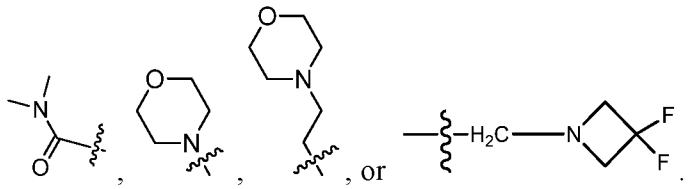
wherein the C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and the -OC_{1-6}alkyl of any of the R^{9A} and R^{10} substituents is unsubstituted or substituted by 1, 2 or 3 R^{12} substituents independently selected from OH, halo, -(=O), -OC_{1-6}alkyl, -C_{1-6}alkyl, -NR^aR^b, -$SiR^aR^bR^c$, a 6- to 12-membered aryl or heteroaryl, or a 3- to 12-membered monocyclic or bicyclic heterocycloalkyl group, where the heteroaryl or heterocycloalkyl groups have 1, 2, 3 or 4 heteroatoms independently selected from O, N or S, and the heterocycloalkyl groups may include a C=O group.

80. The compound of any one of embodiments 1, 49-76, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the

pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^9 is independently selected from H, -OH, -CH_3, -CH_2CH_3, -C(=O)CH_3, -$CH_2C(=O)OCH_2CH_3$,  .

81. The compound of embodiment 80, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^9 is H.

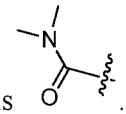
82. The compound of embodiment 80, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^9 is –CH_3.

83. The compound of any one of embodiments 1, 49-75, or 77-80, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is independently selected from H, -OH, -CH_3, -CH_2CH_3, -$OCH_2C(=O)OCH_2CH_3$,  .

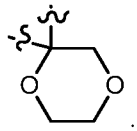
84. The compound of embodiment 83, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is H.

85. The compound of embodiment 83, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is -$C_{1\text{-}6}$alkyl.

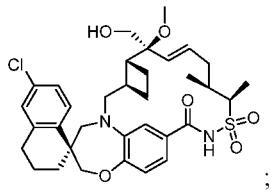
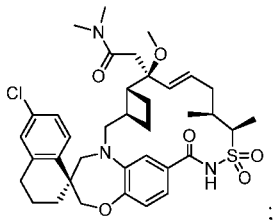
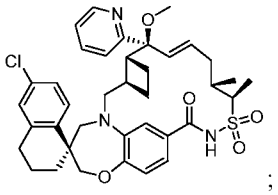
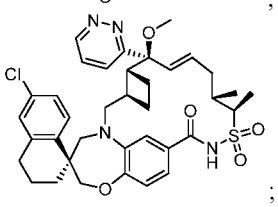
86. The compound of embodiment 83, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is –CH_3.

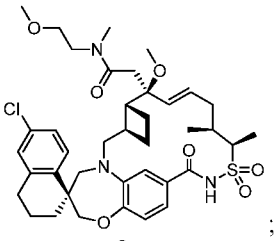
87. The compound of embodiment 83, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^{9A} is  .

88. The compound of any one of embodiments 1, 49-75 and 78, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein alternatively R^9 and R^{9A} together with the atoms to which they are bonded may form a 5- to 12-membered monocyclic or bicyclic ring, optionally containing a heteroatom in addition to Q selected from N, O or S atom, further wherein the 5-12 membered ring may contain a double bond.

89. The compound of embodiment 88, or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof, wherein R^9 and R^{9A} together with Q, W and the C to which Q and W are bonded form  .

90. Another embodiment of the present invention comprises a compound, wherein the compound has a structure selected from:

 ;
 ;
 ;
 ;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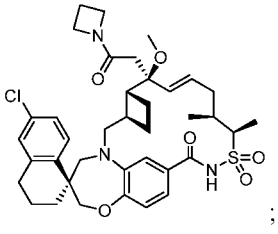
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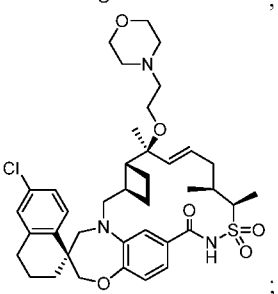
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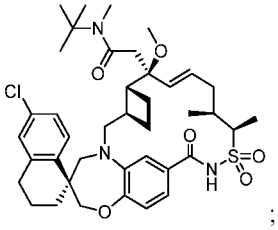
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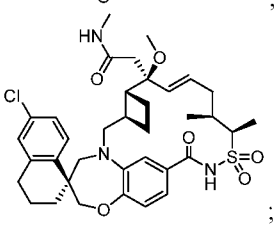
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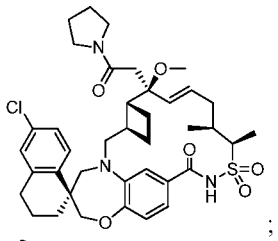
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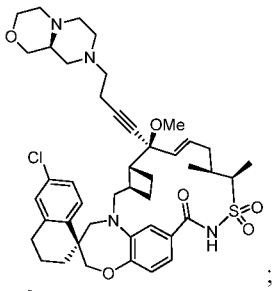
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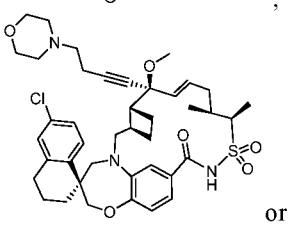
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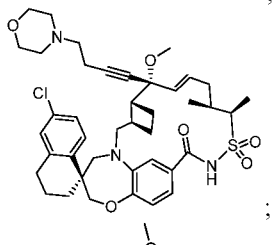
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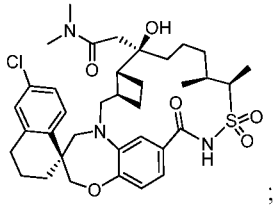
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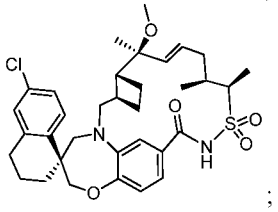
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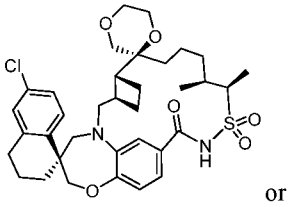
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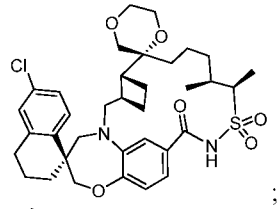
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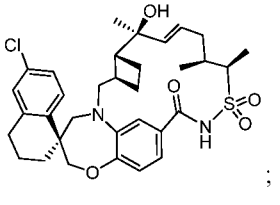
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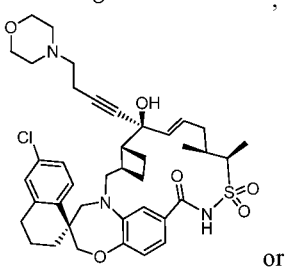
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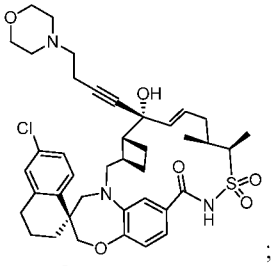
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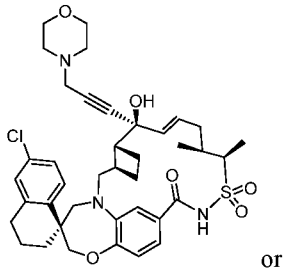
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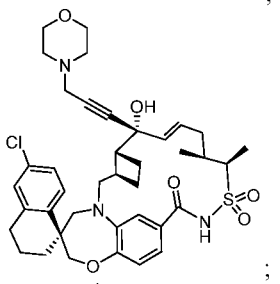
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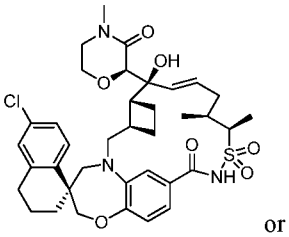
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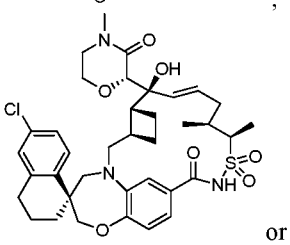
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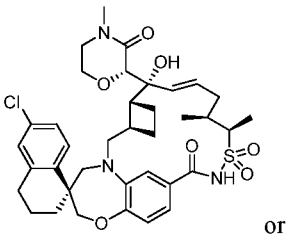
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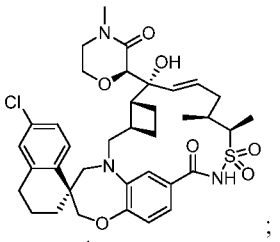
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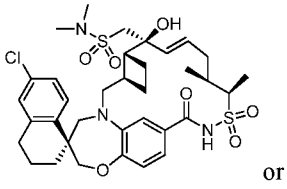
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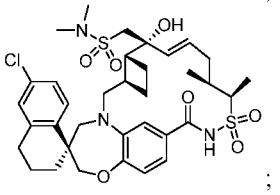
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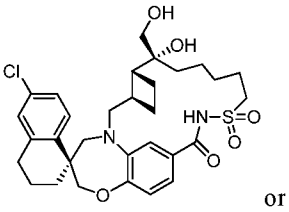
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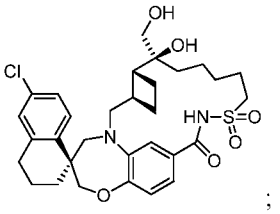
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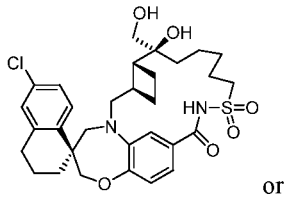

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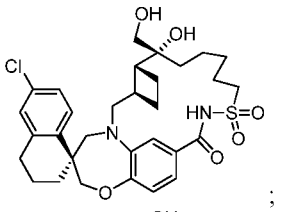

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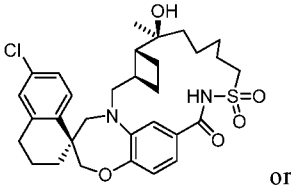

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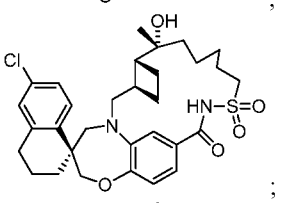

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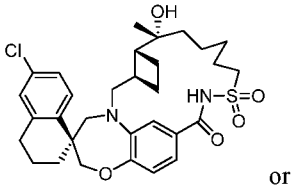

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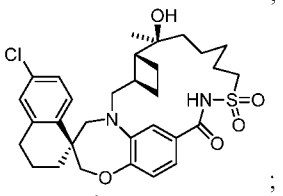

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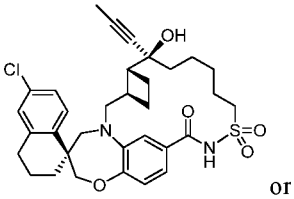

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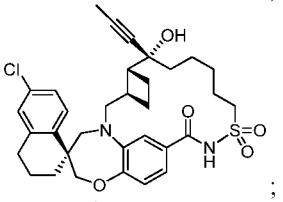

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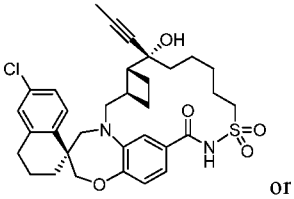

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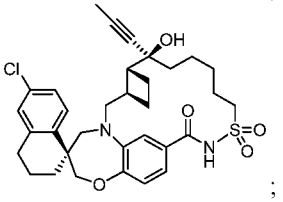

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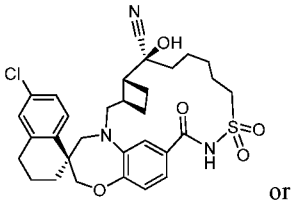

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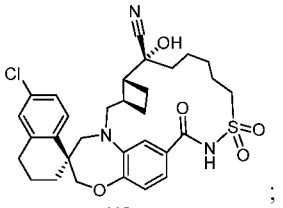

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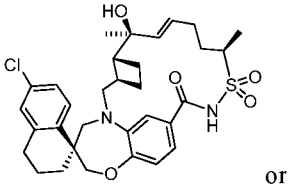

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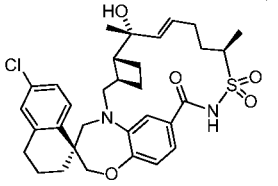

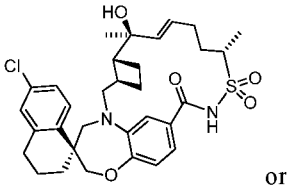

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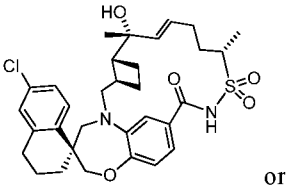

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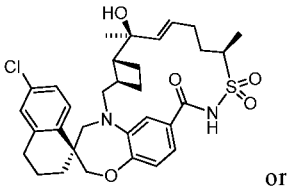
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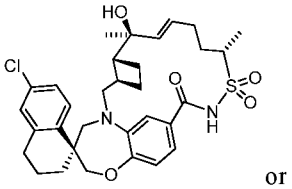
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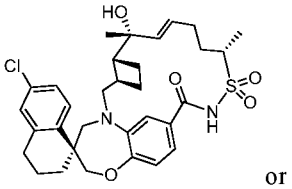
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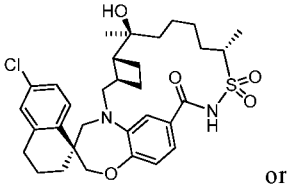
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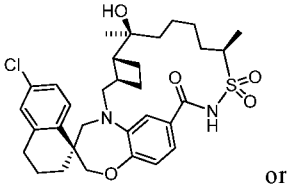
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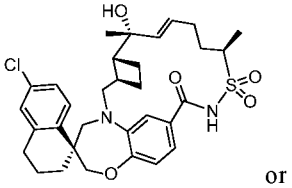
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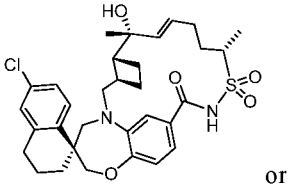
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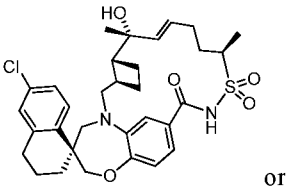
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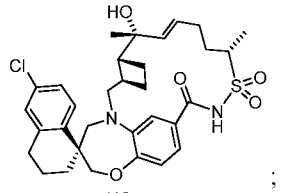
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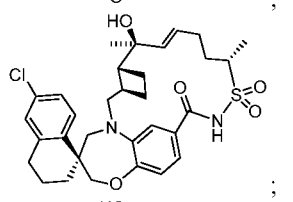
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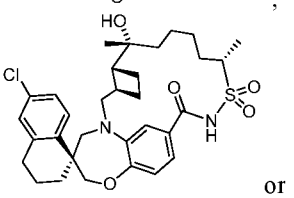
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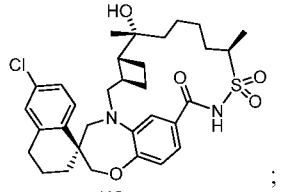
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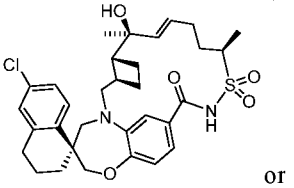
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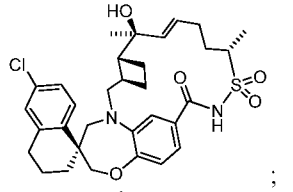
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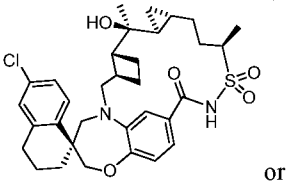
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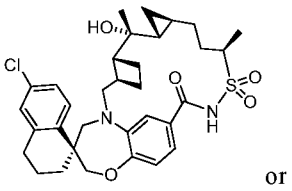
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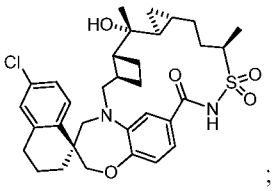
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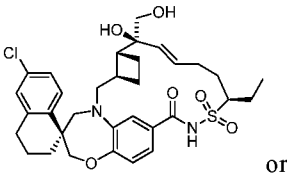
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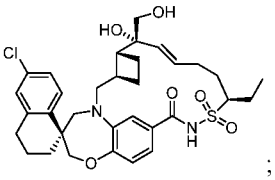
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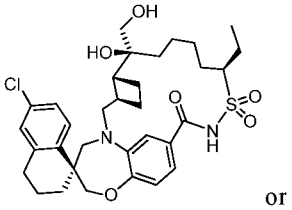
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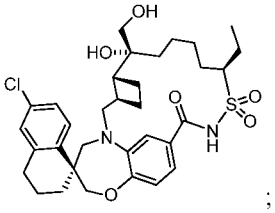
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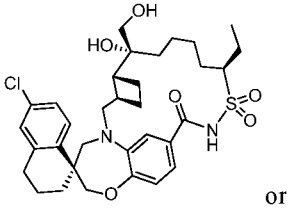
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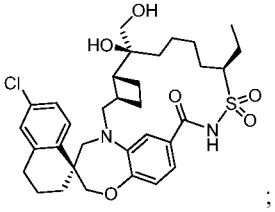
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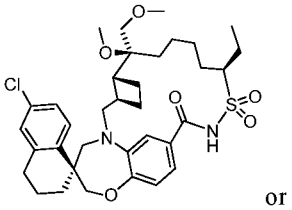
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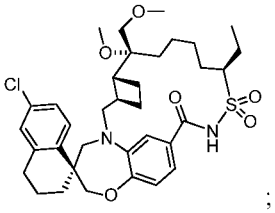
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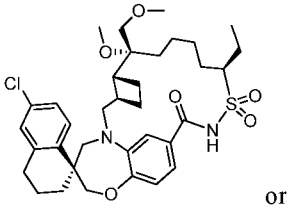
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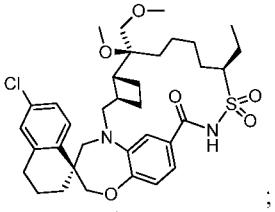
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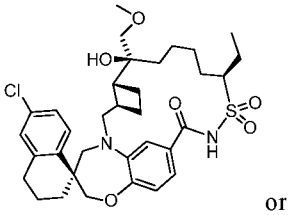
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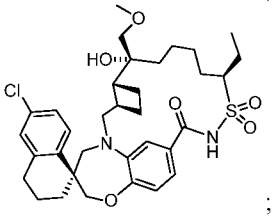
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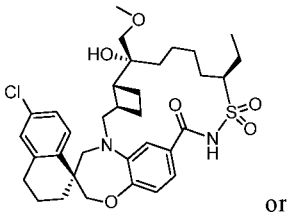
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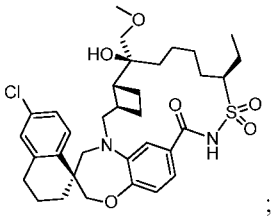
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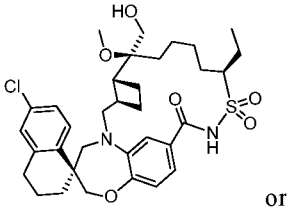
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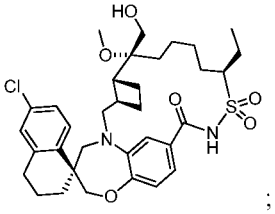
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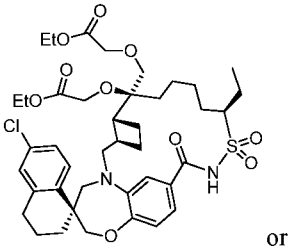
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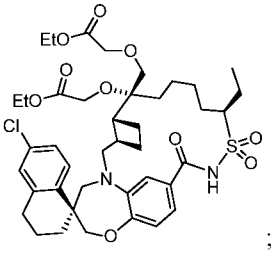
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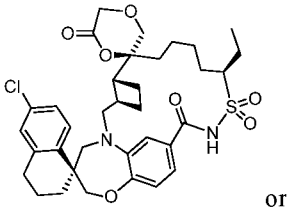
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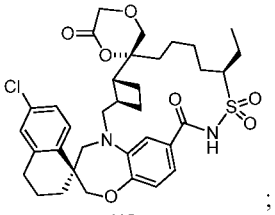
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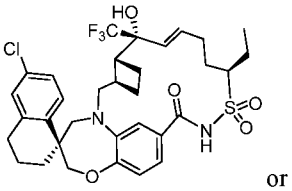
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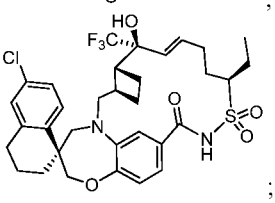
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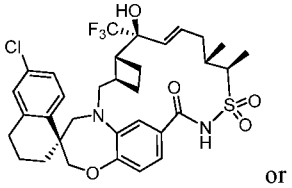
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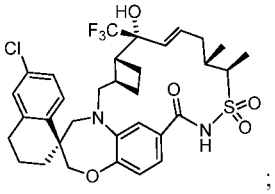
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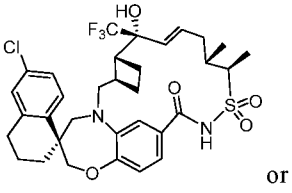
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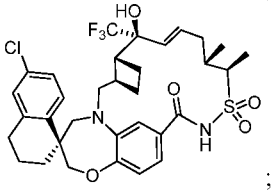
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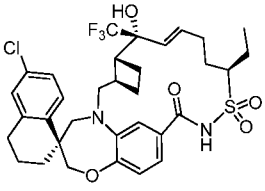
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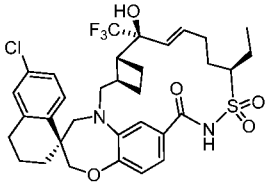
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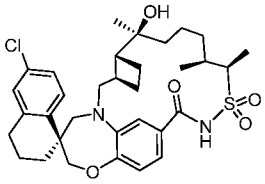
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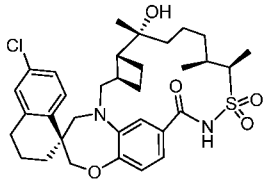
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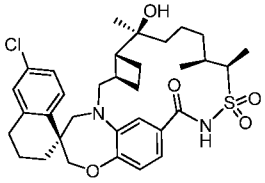
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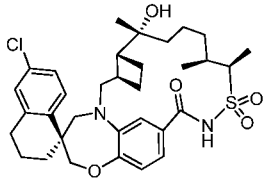
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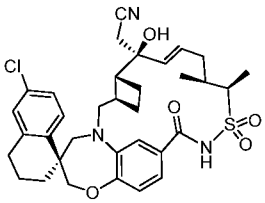
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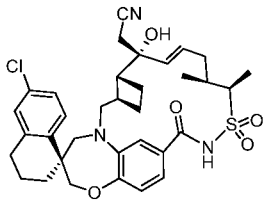
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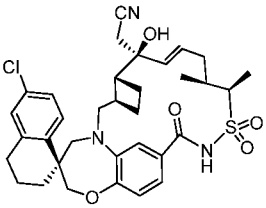
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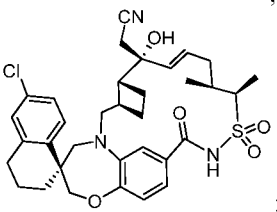
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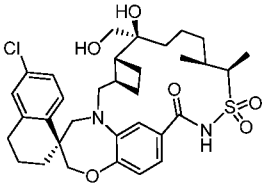
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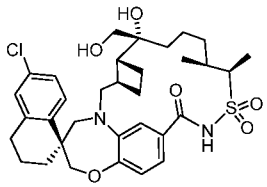
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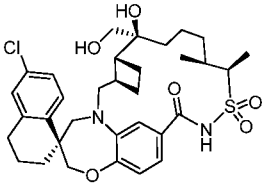
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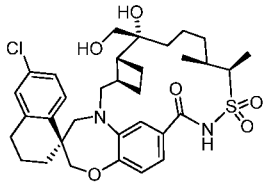
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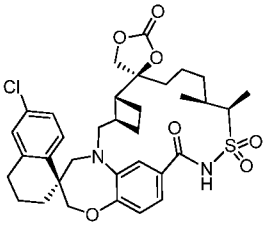
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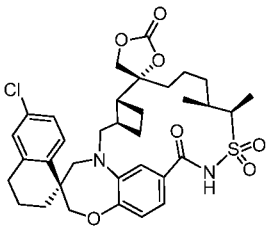
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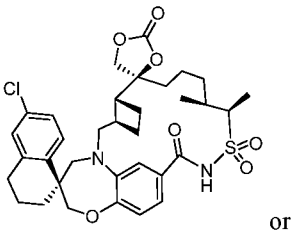
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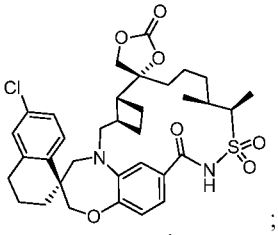
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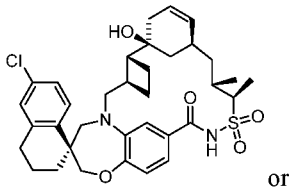
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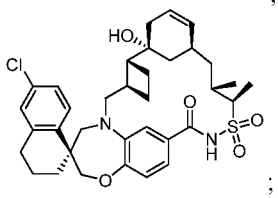
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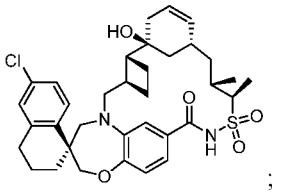
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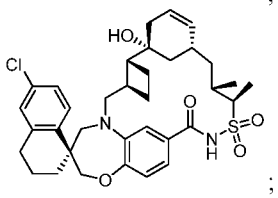
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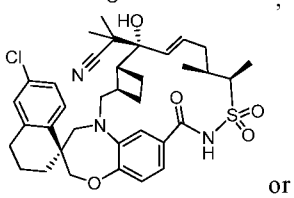
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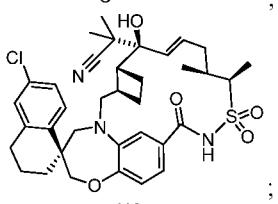
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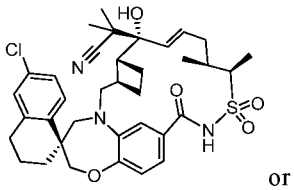
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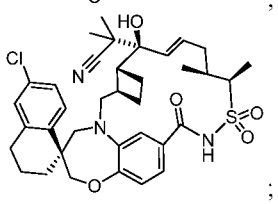
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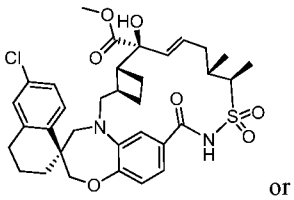
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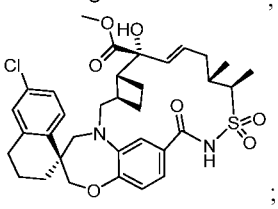
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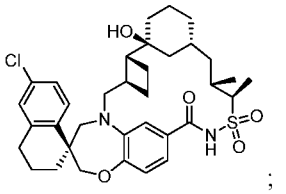
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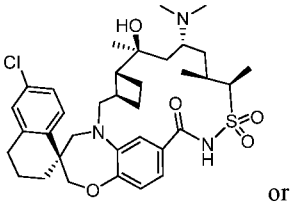
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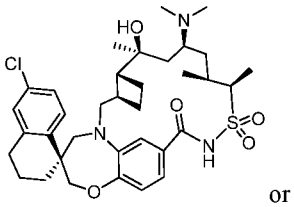
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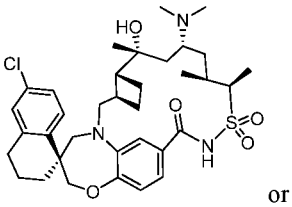
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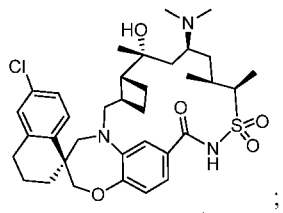
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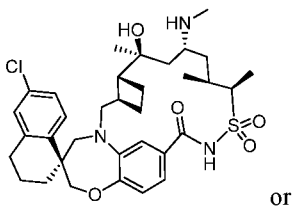
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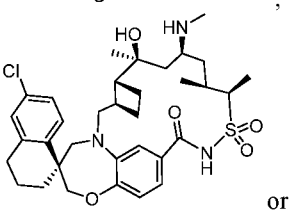
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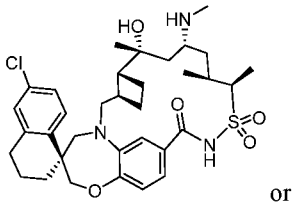
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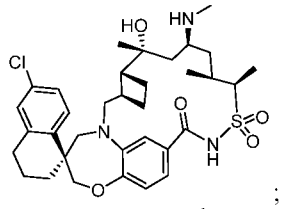
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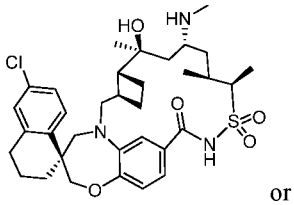
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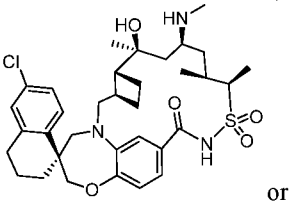
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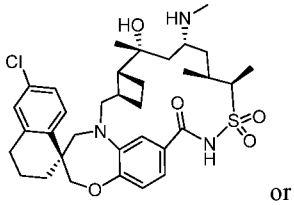
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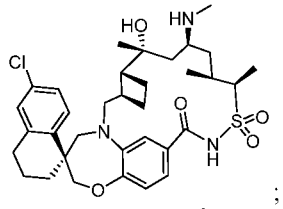
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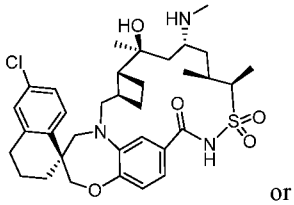
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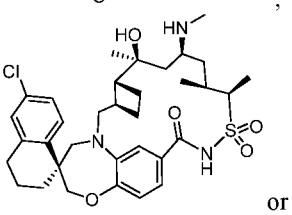
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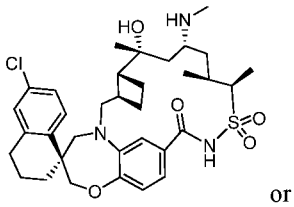
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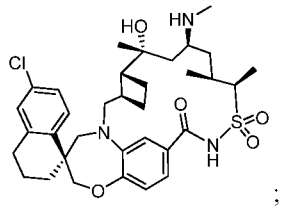
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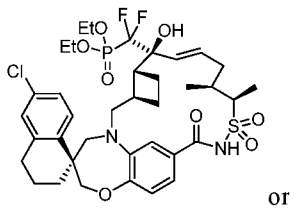
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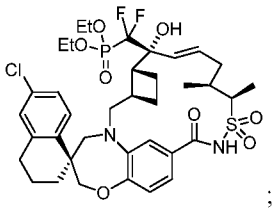
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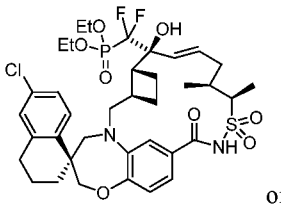
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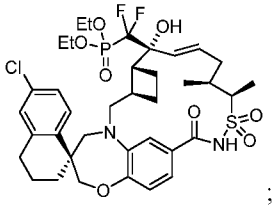
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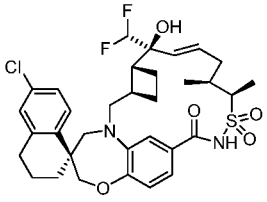
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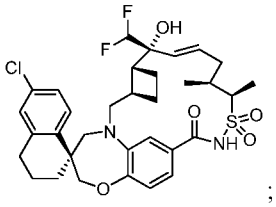
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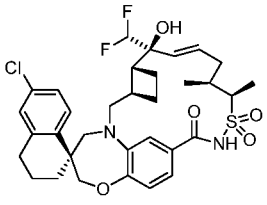
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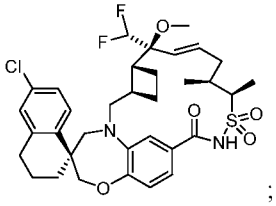
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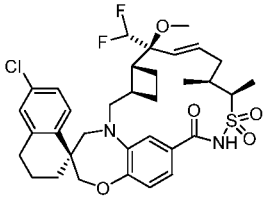
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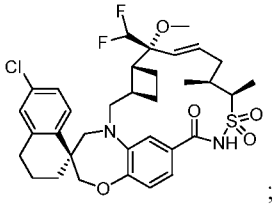
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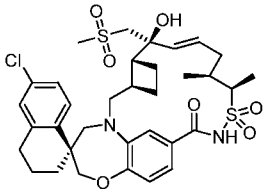
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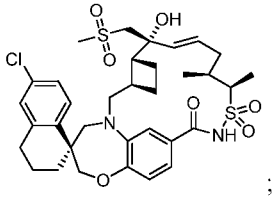
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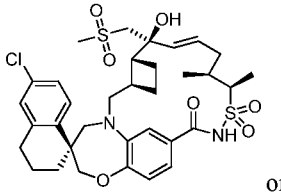
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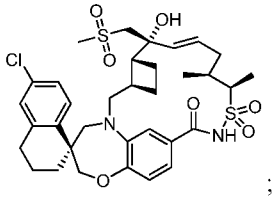
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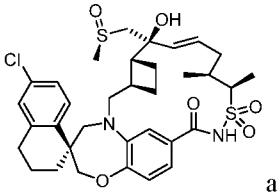
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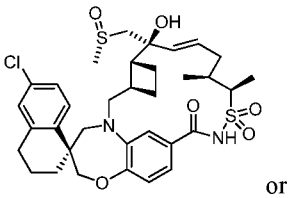
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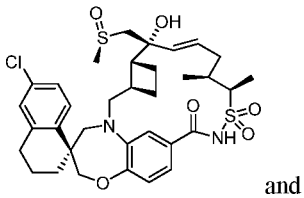
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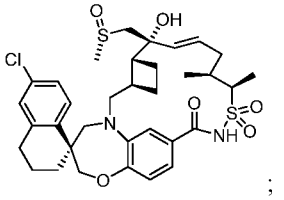
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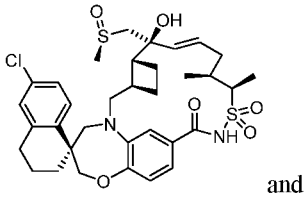
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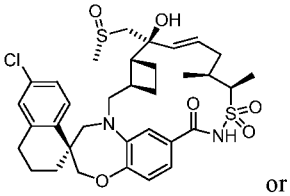
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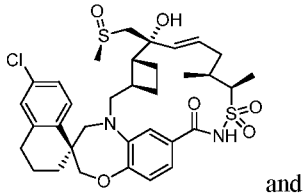
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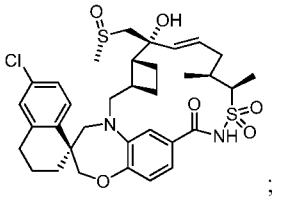
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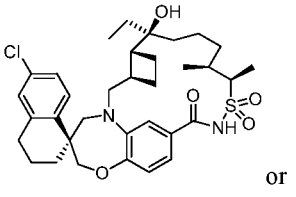
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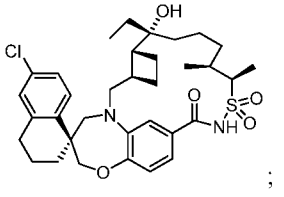
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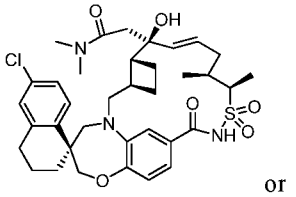
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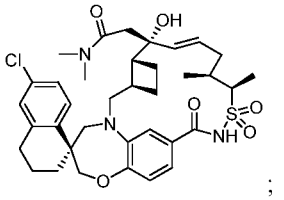
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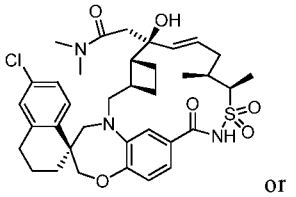
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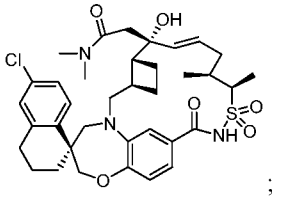
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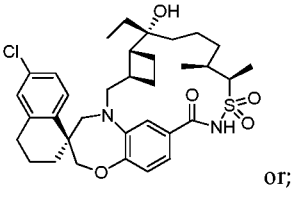
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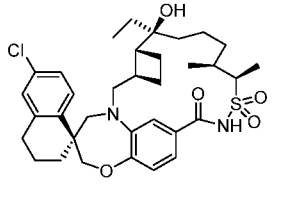

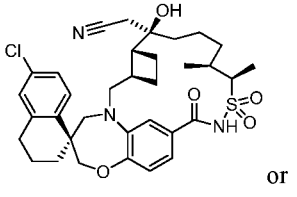
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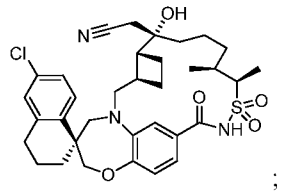
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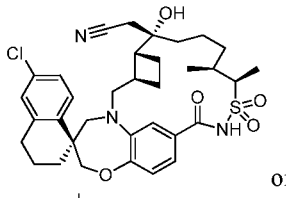
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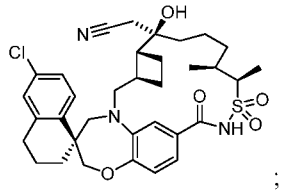
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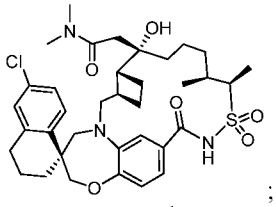
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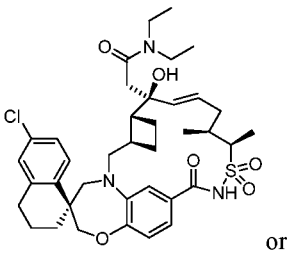
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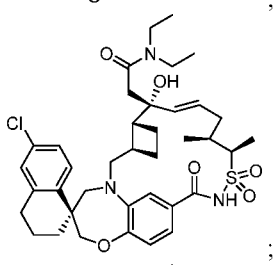
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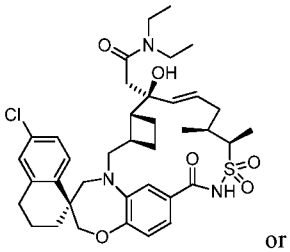
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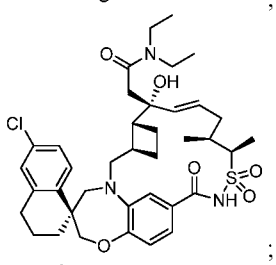
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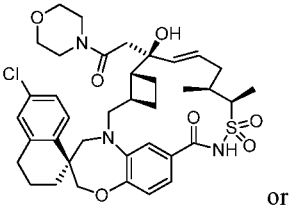
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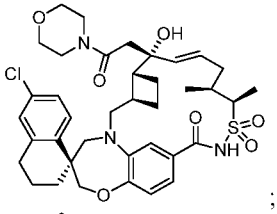
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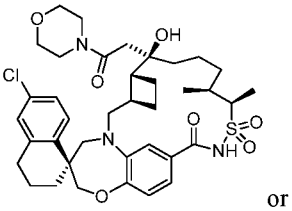
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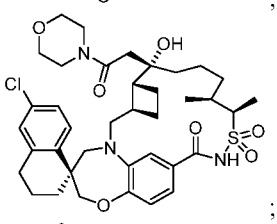
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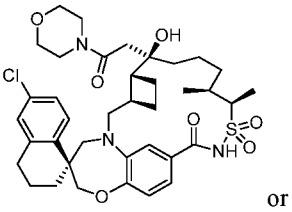
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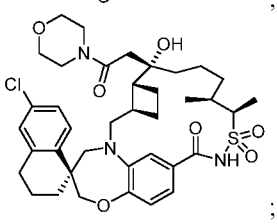
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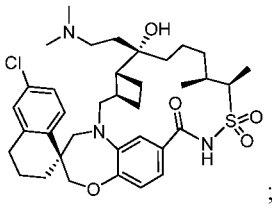
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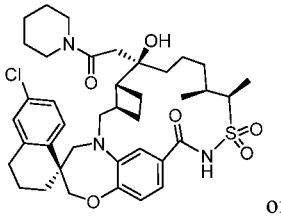
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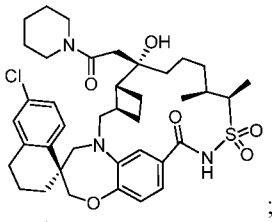
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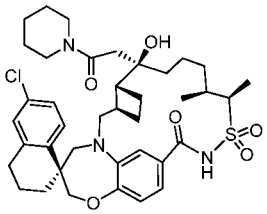
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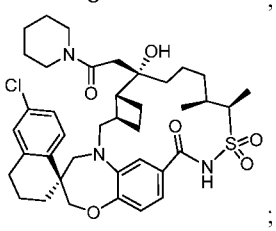
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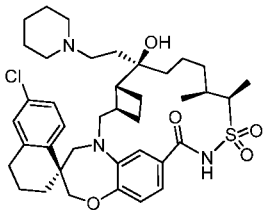
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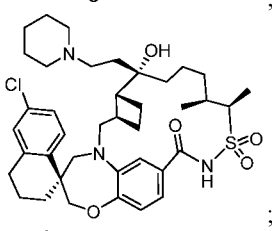
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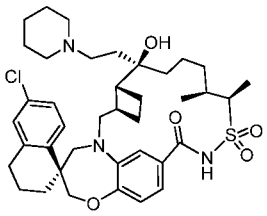
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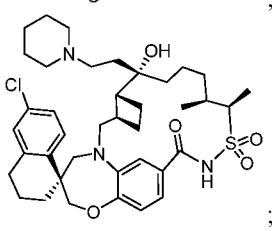
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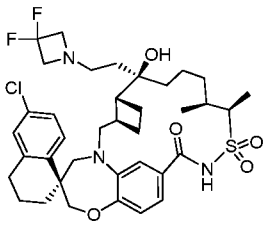
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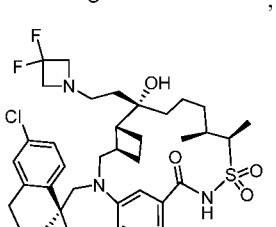
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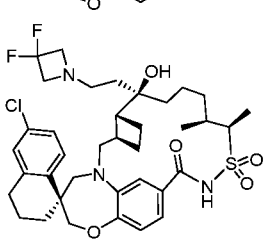
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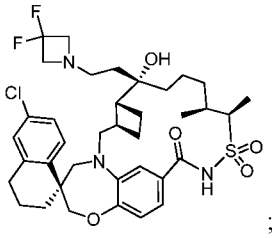
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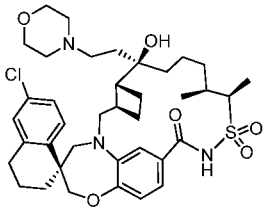
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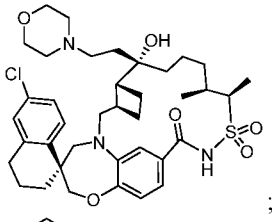
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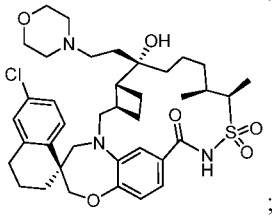
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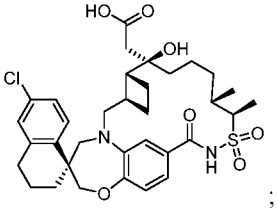
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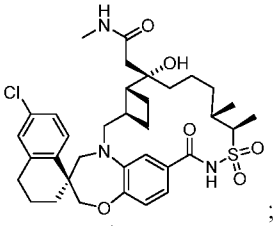
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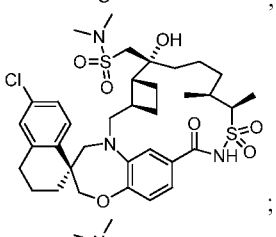
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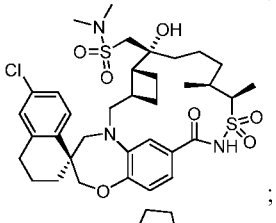
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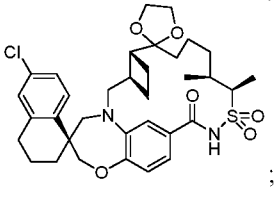
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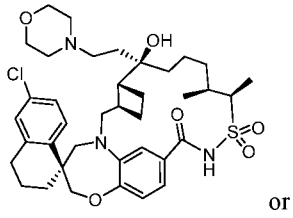
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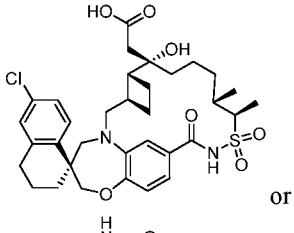
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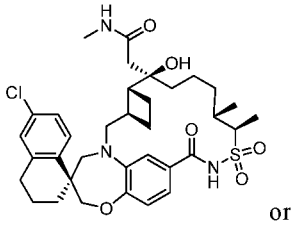
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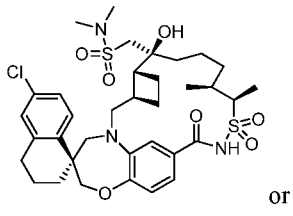
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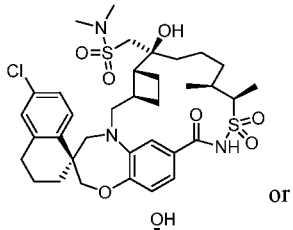
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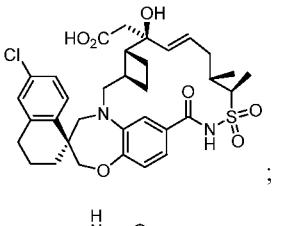
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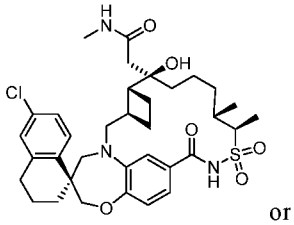
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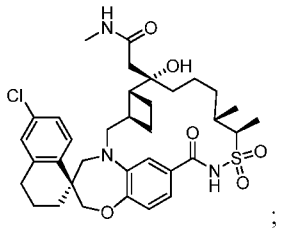
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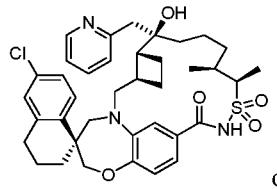
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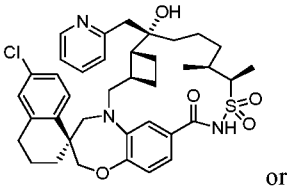
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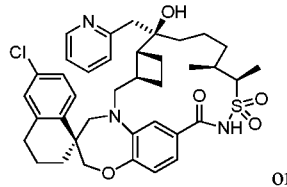
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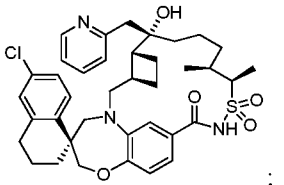
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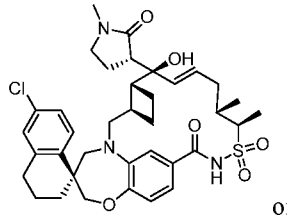
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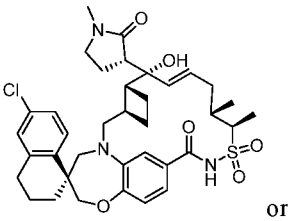
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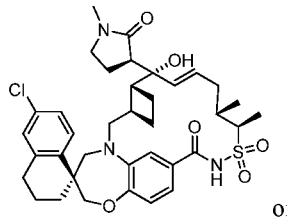
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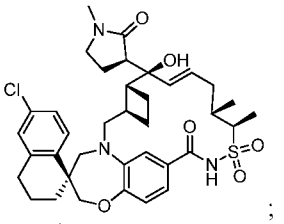
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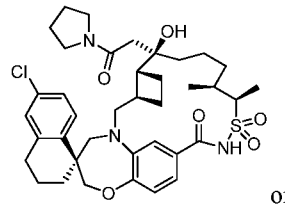
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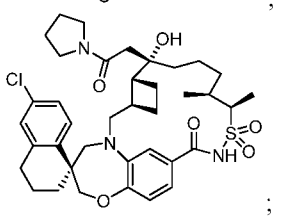
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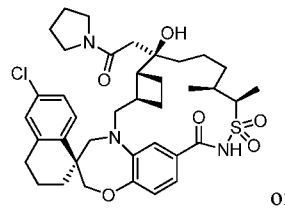
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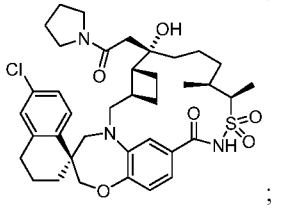
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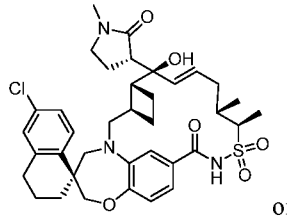
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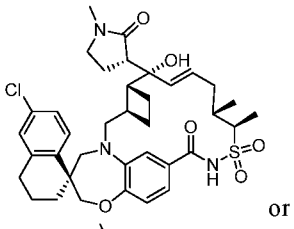
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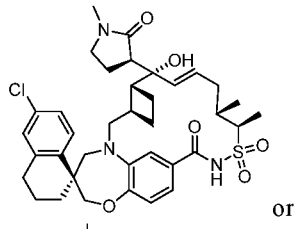
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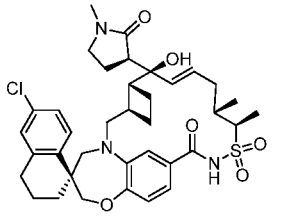
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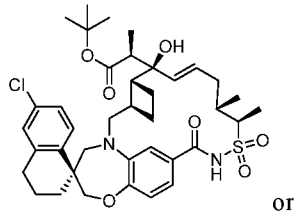
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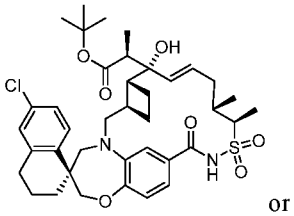
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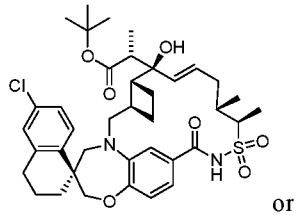
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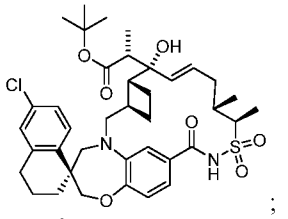
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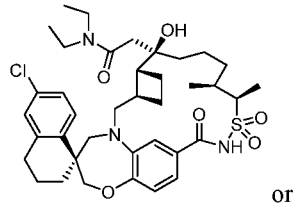
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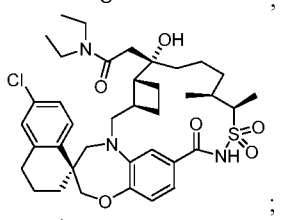
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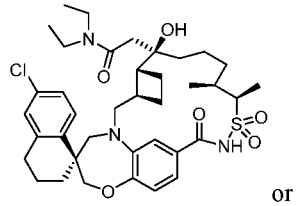
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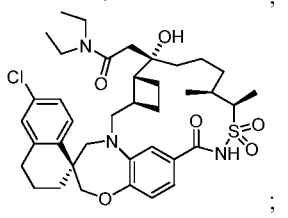
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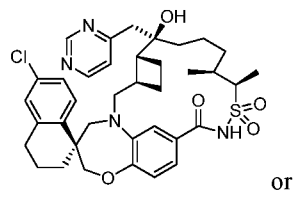
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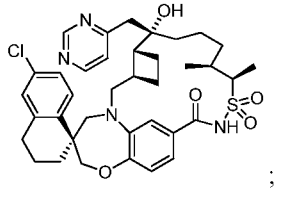
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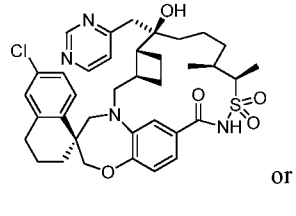
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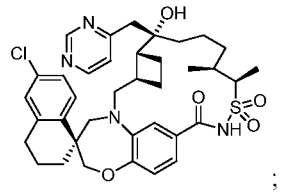
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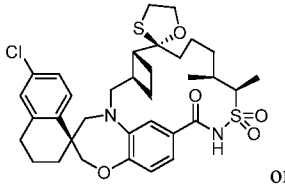
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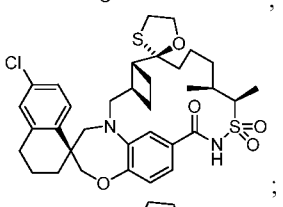
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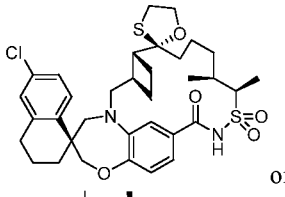
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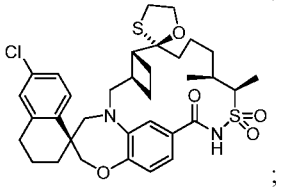
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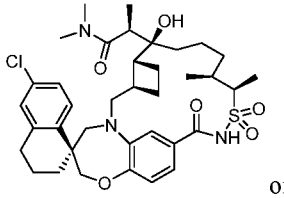
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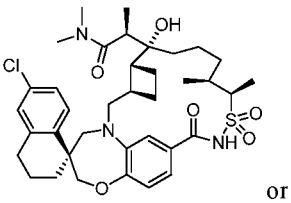
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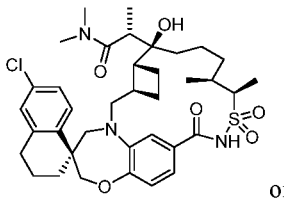
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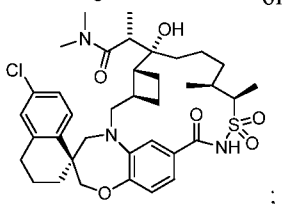
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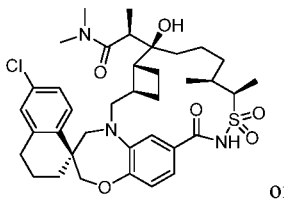
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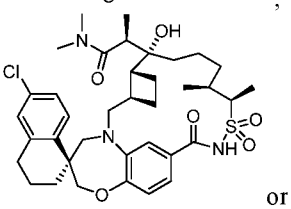
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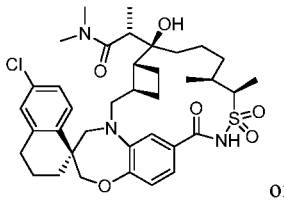
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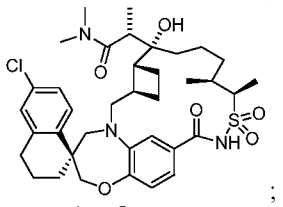
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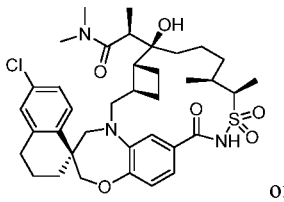
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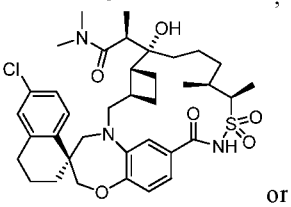
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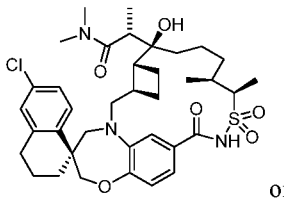
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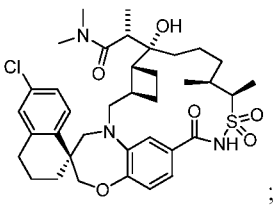
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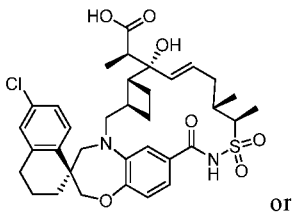
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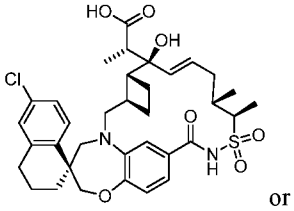
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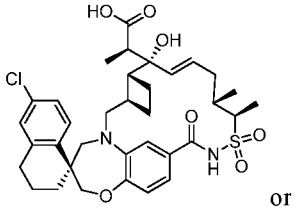
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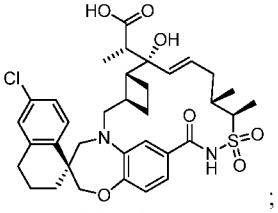
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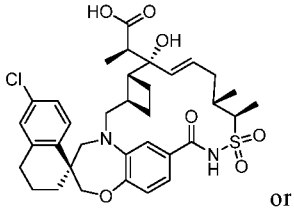
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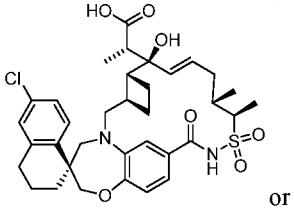
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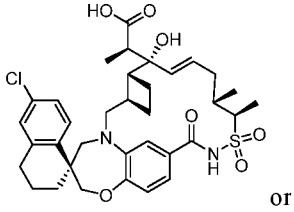
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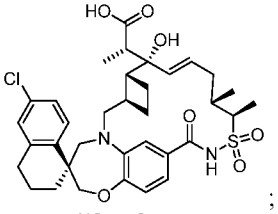
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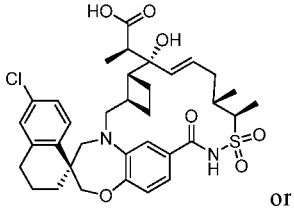
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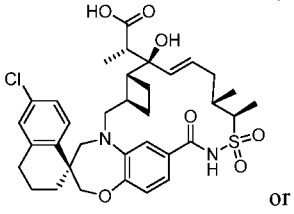
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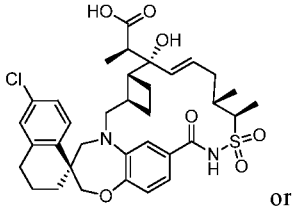
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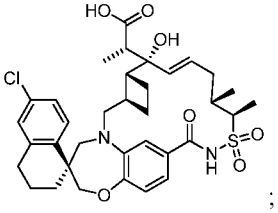
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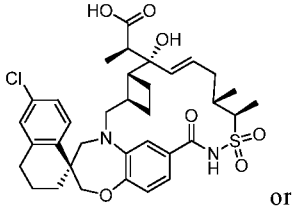
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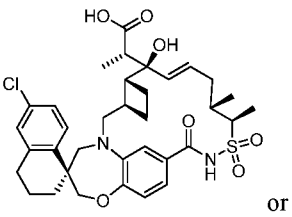
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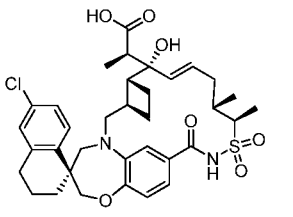
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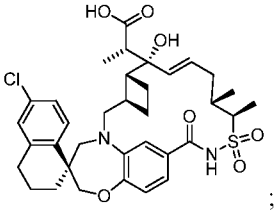
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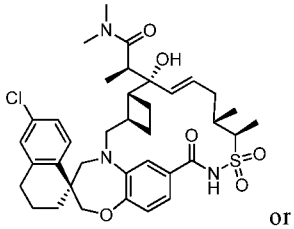
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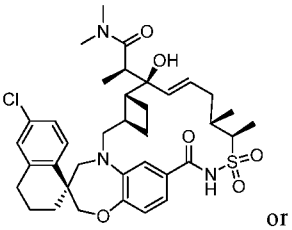
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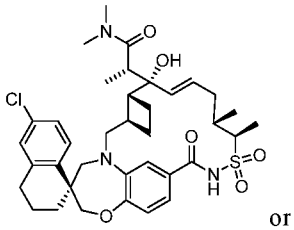
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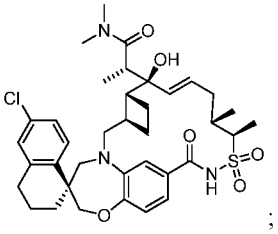
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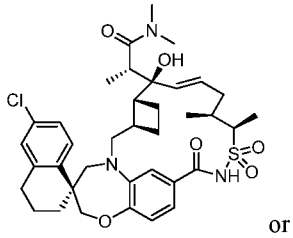
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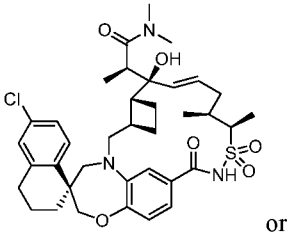
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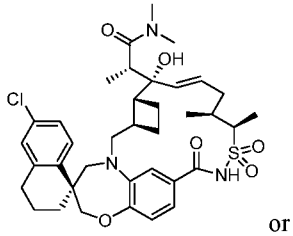
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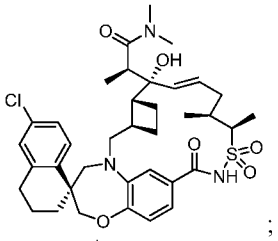
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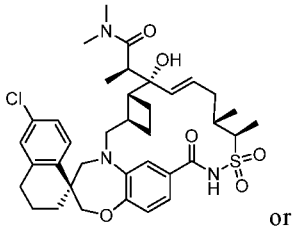
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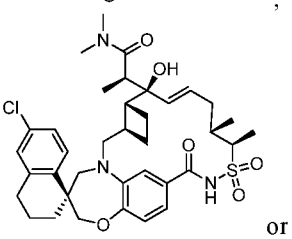
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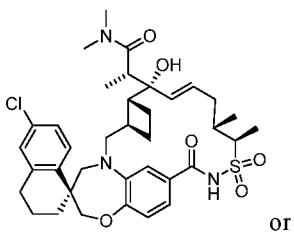
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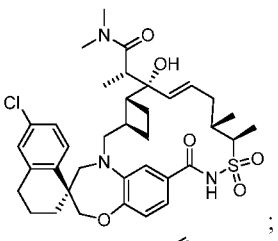
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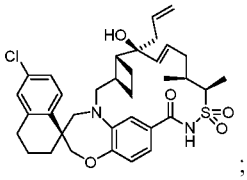
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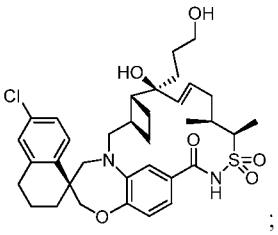
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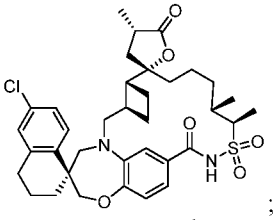
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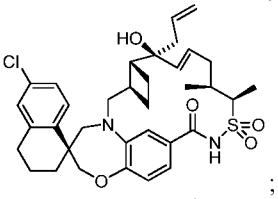
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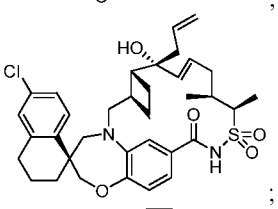
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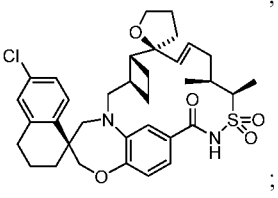
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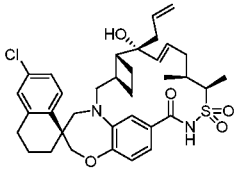
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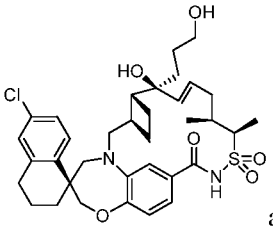
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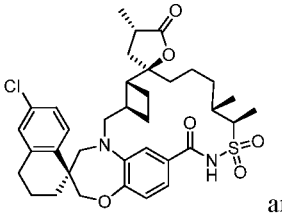
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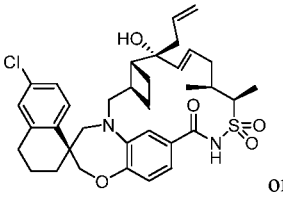
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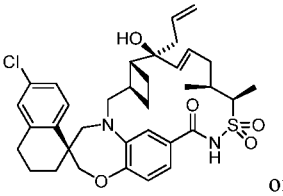
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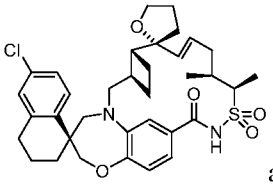
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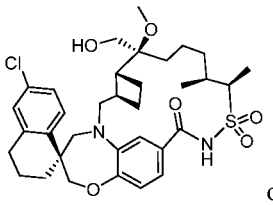
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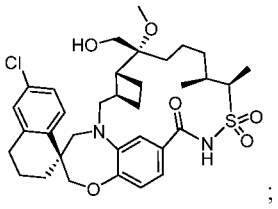
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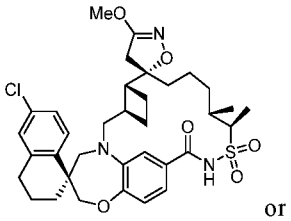
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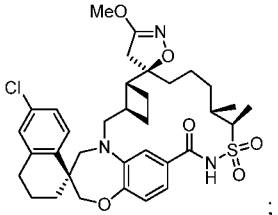
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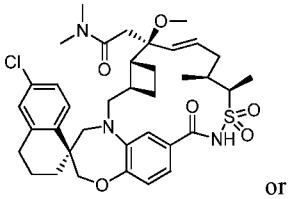
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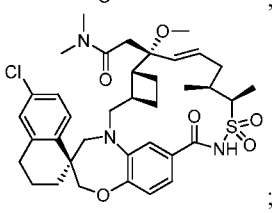
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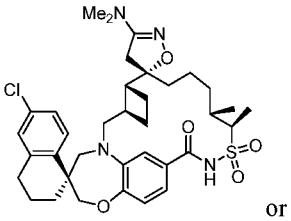
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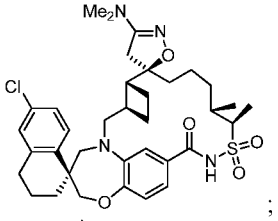
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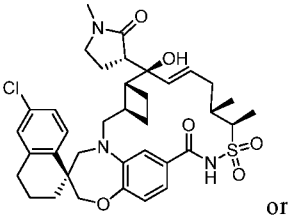
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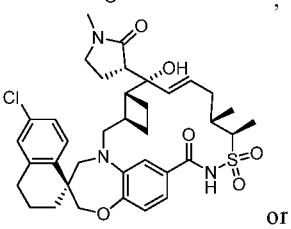
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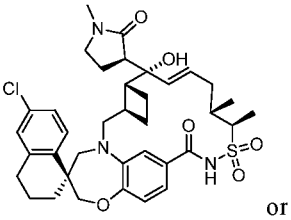
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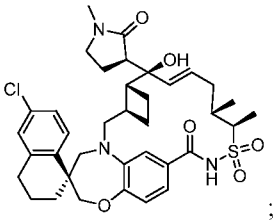
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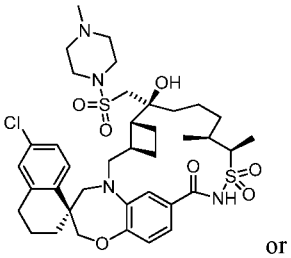
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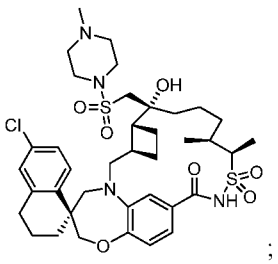
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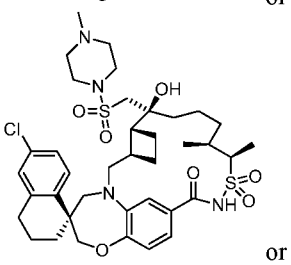
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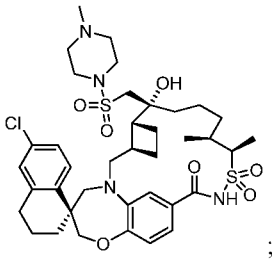
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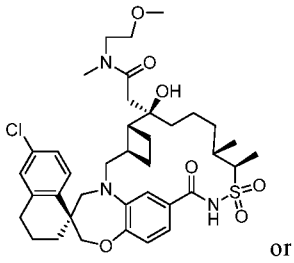
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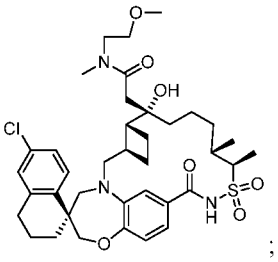
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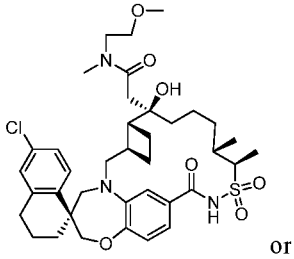
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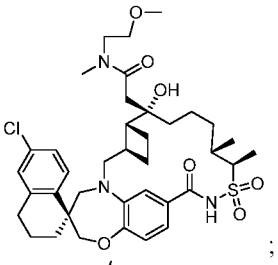
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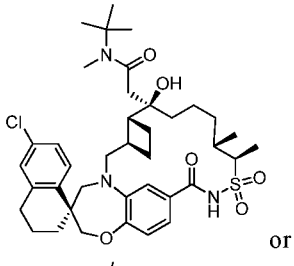
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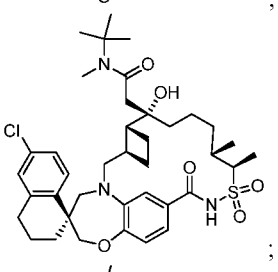
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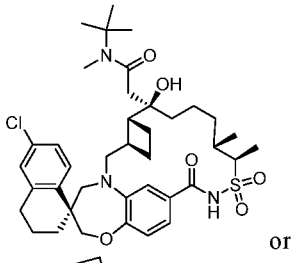
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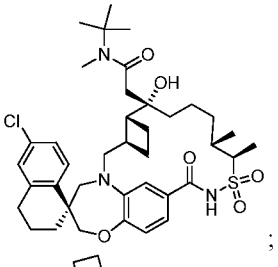
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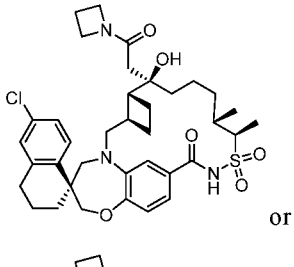
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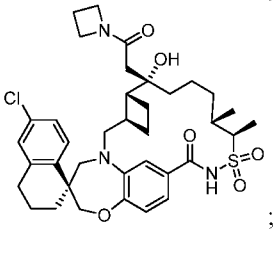
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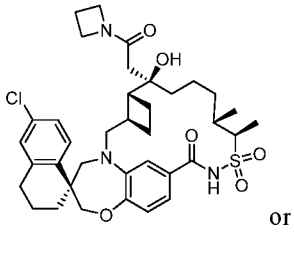
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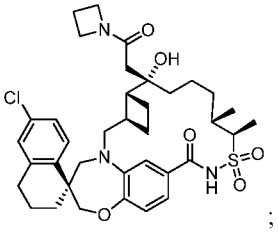
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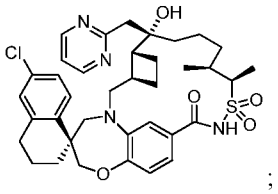
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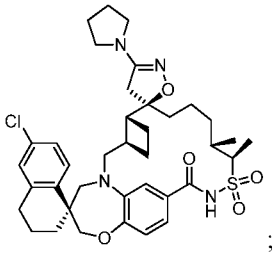
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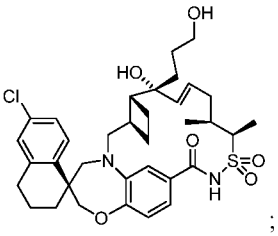
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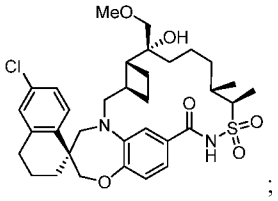
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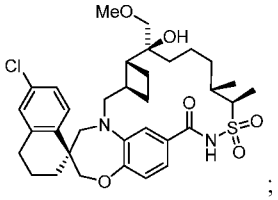
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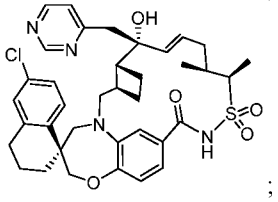
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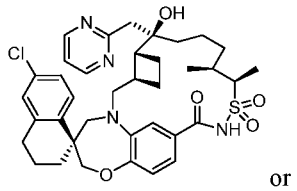
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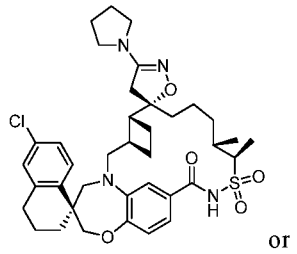
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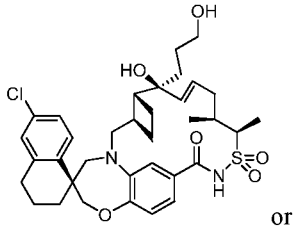
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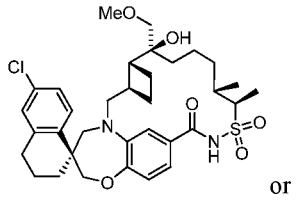
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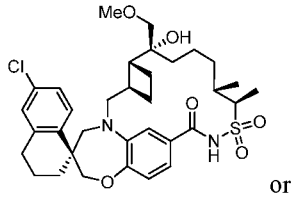
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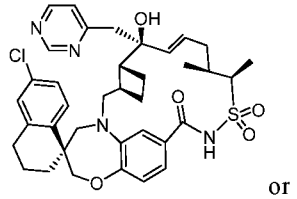
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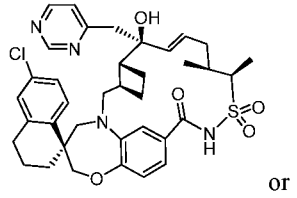
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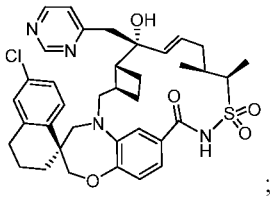
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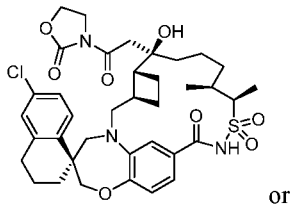
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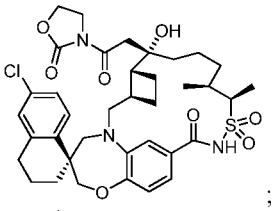
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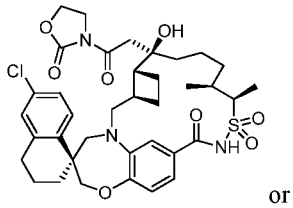
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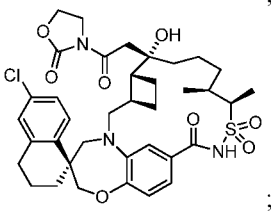
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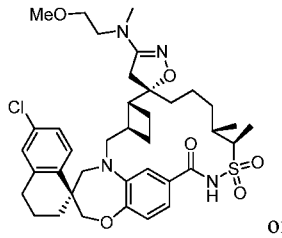
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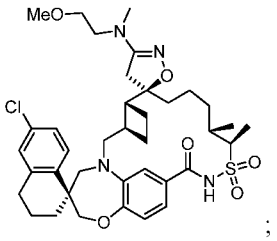
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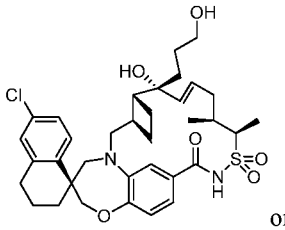
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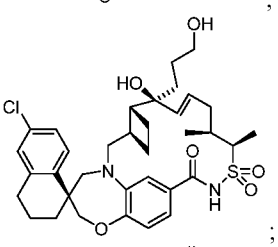
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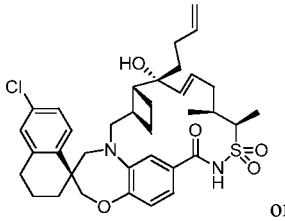
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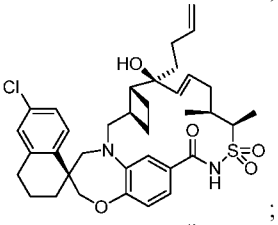
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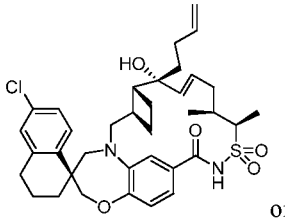
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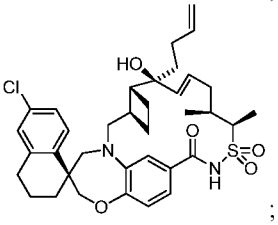
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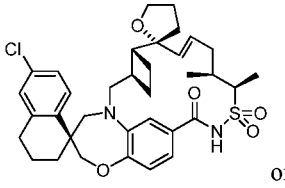
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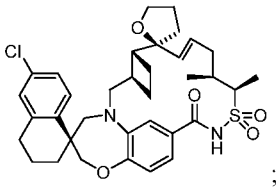
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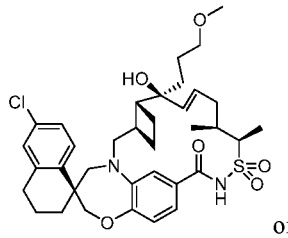
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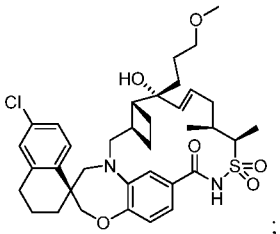
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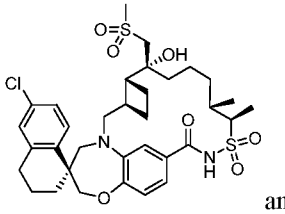
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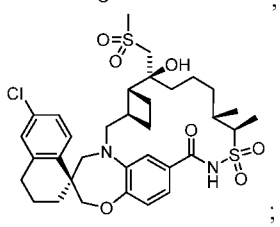
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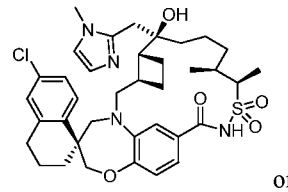
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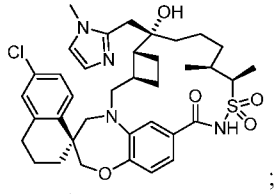
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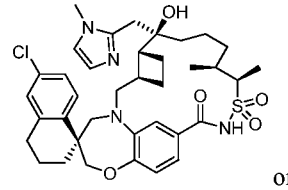
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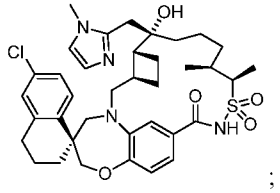
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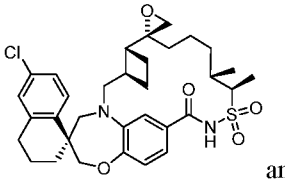
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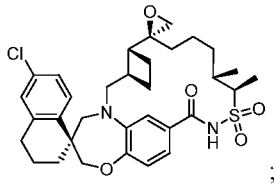
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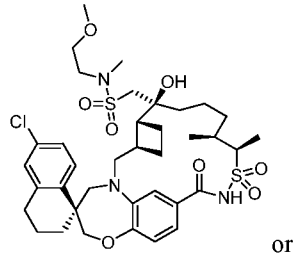
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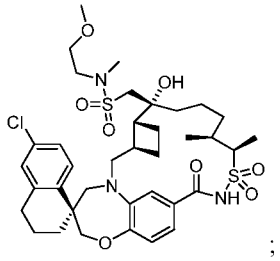
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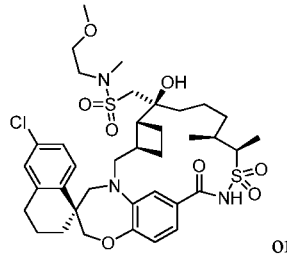
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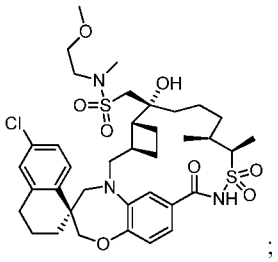
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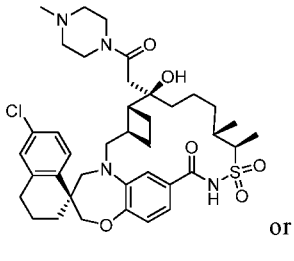
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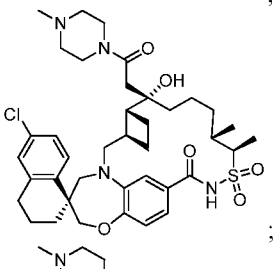
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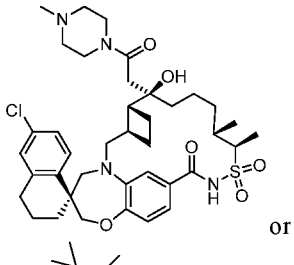
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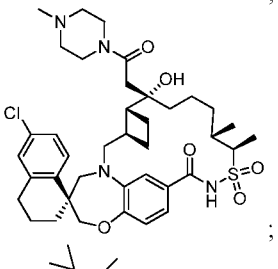
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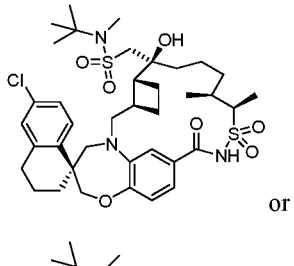
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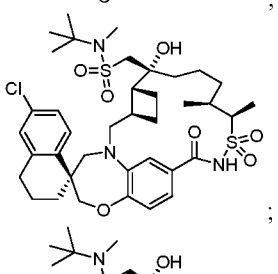
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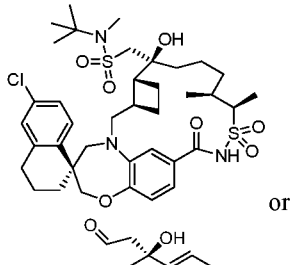
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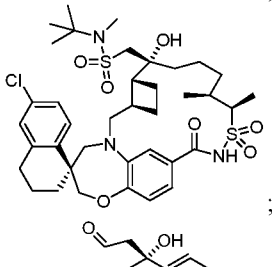
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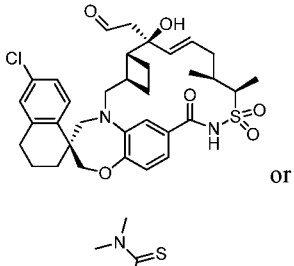
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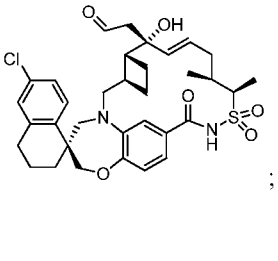
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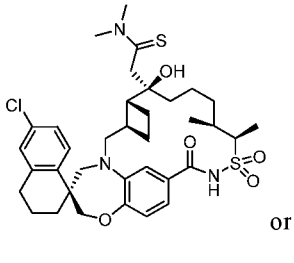
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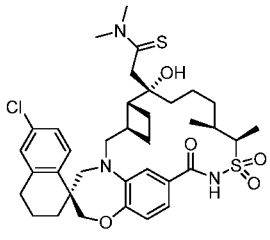
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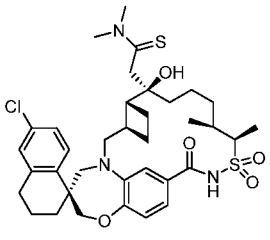
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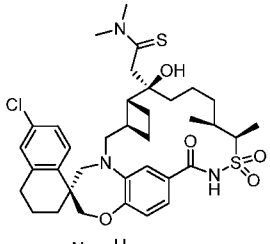
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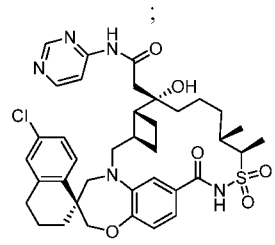
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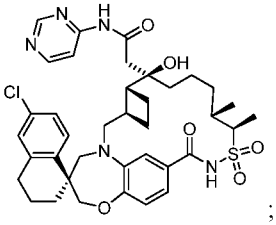
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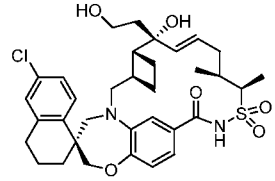
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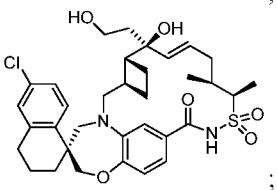
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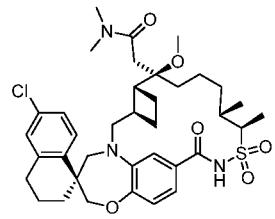
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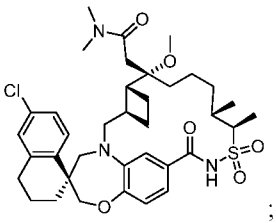
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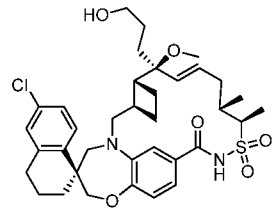
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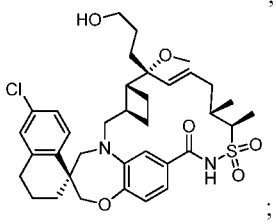
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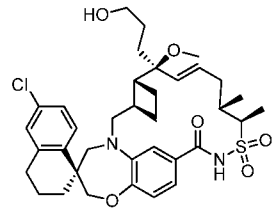
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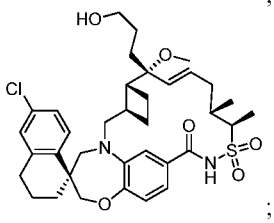
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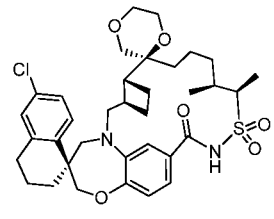
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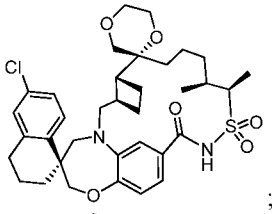
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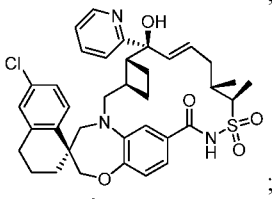
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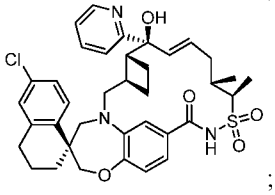
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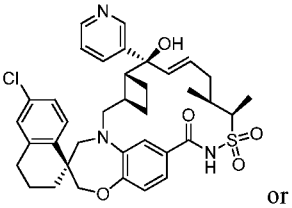
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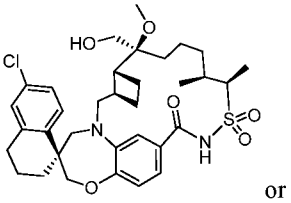
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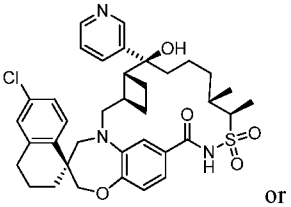
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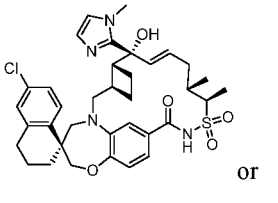
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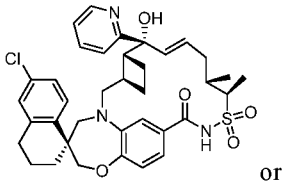
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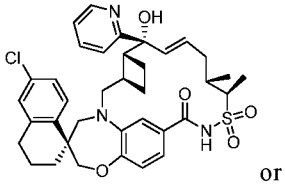
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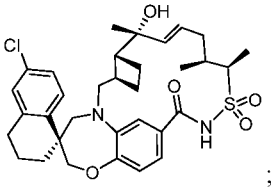
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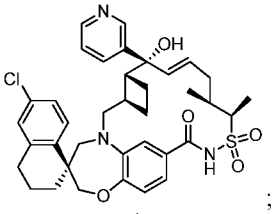
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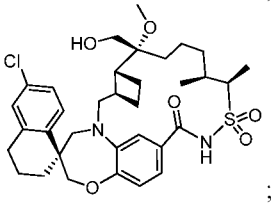
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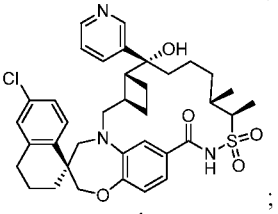
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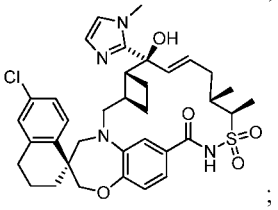
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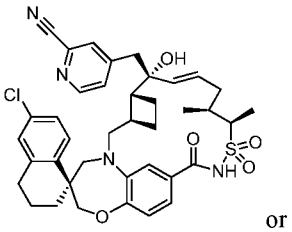
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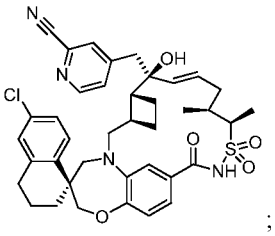
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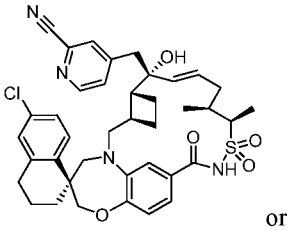
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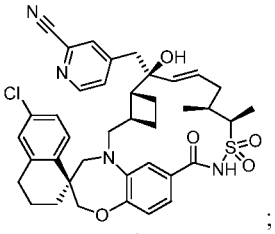
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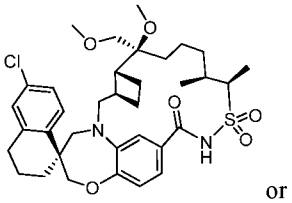
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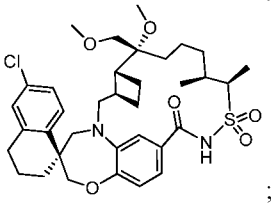
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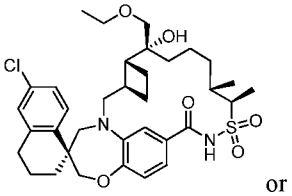
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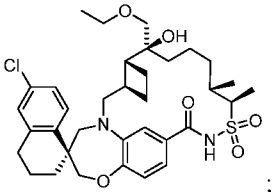
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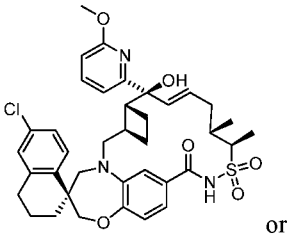
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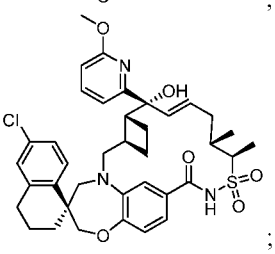
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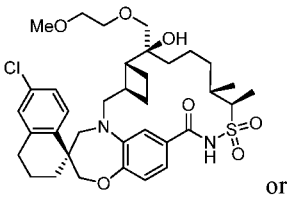
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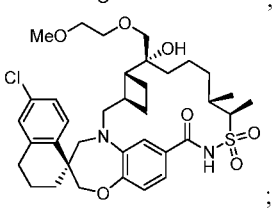
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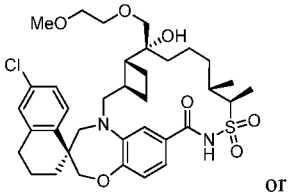
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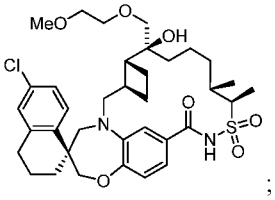
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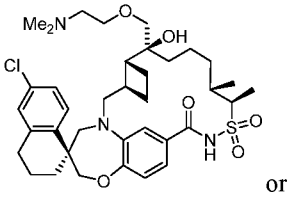
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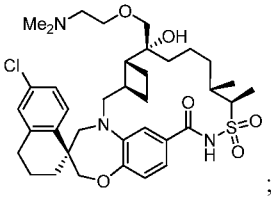
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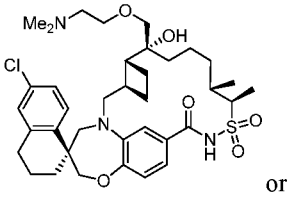
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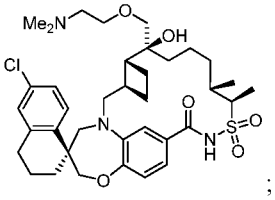
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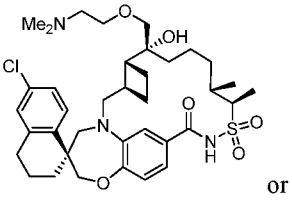
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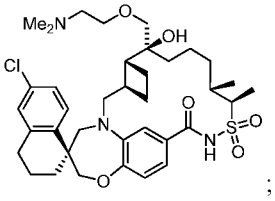
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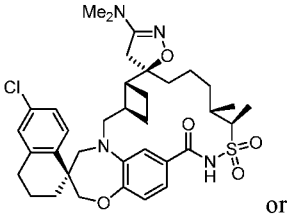
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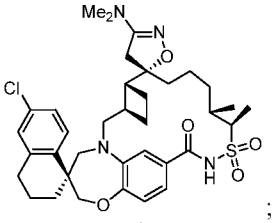
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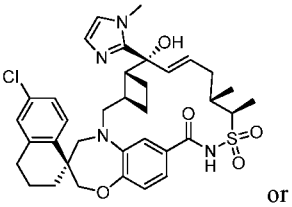
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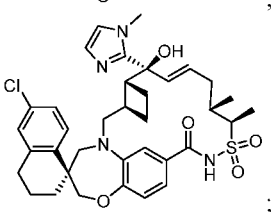
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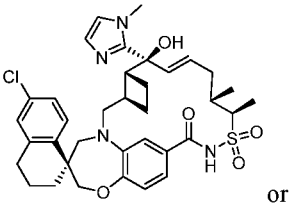
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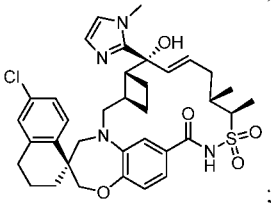
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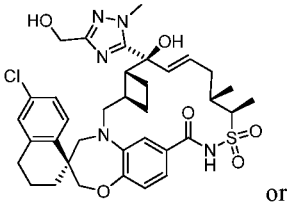
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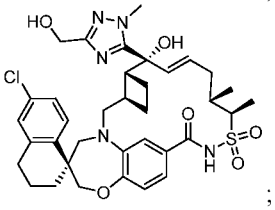
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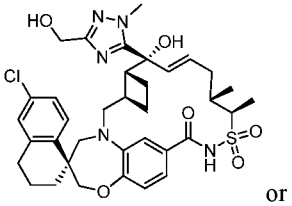
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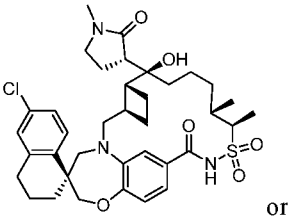
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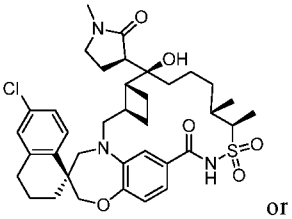
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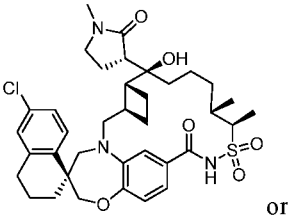
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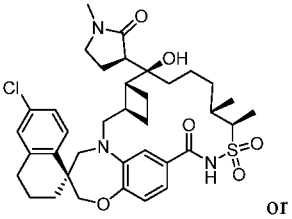
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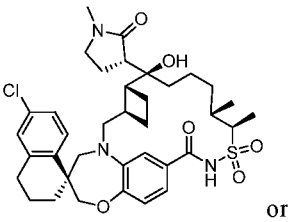
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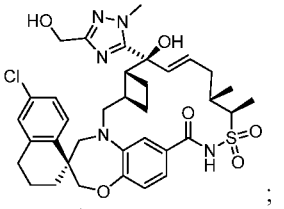
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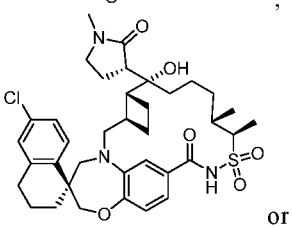
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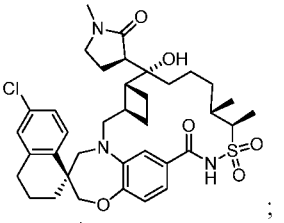
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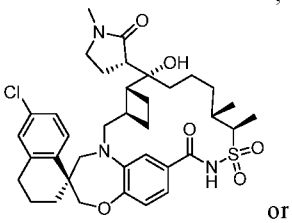
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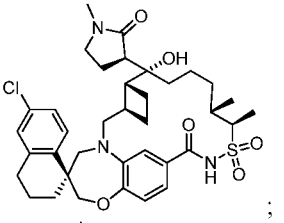
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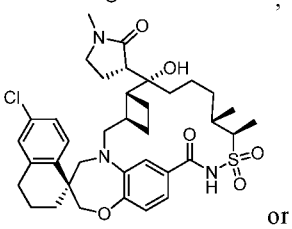
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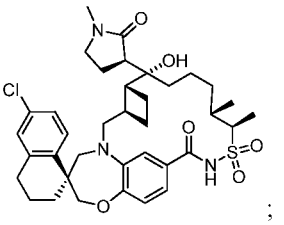
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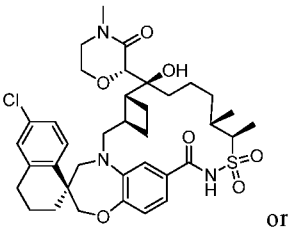
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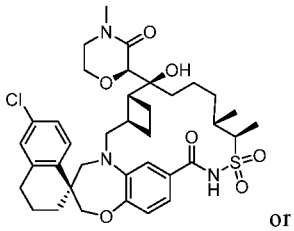
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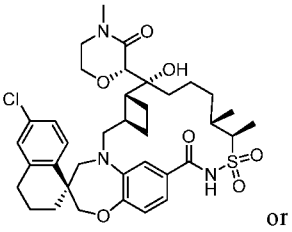
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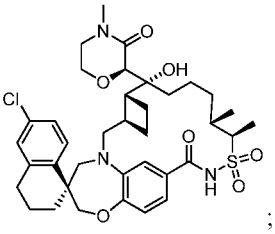
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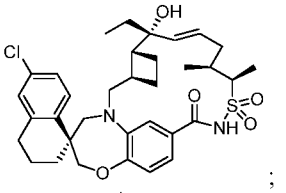
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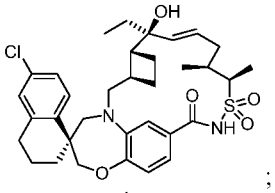
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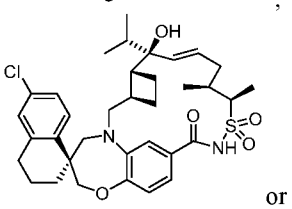
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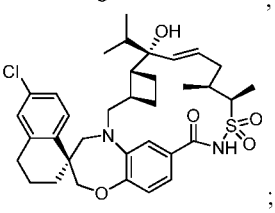
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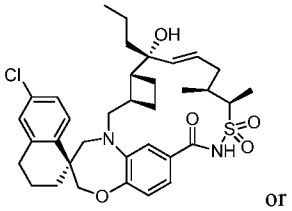
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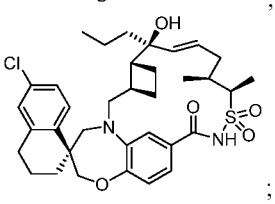
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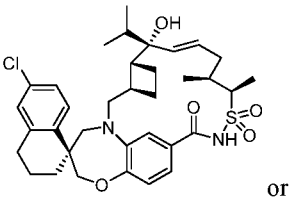
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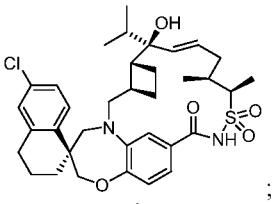
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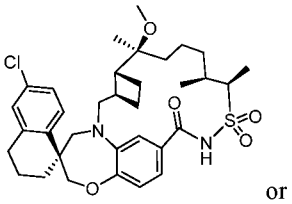
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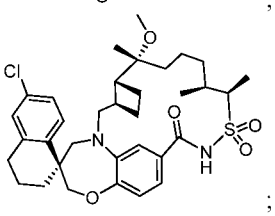
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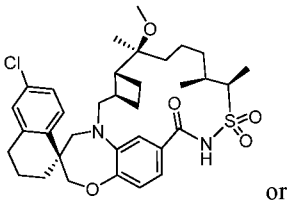
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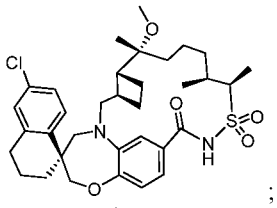
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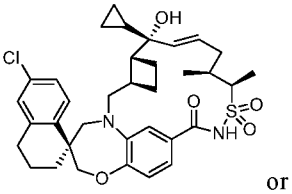
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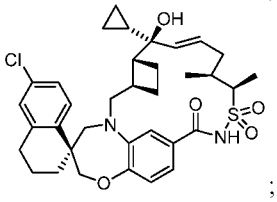
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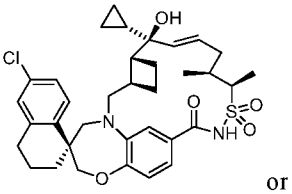
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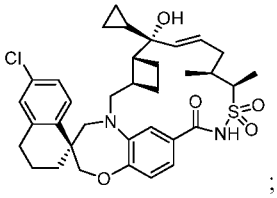
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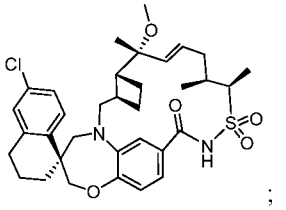
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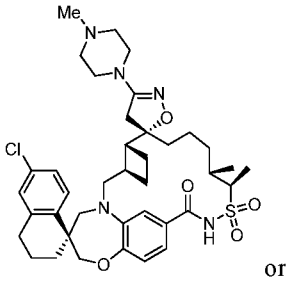
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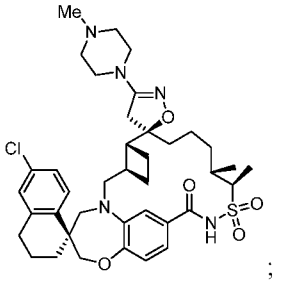
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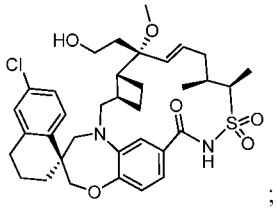
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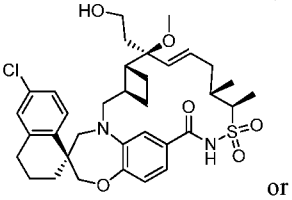
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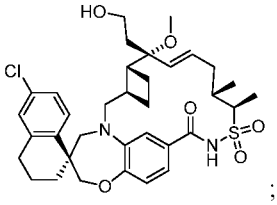
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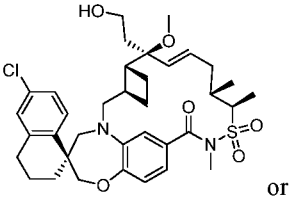
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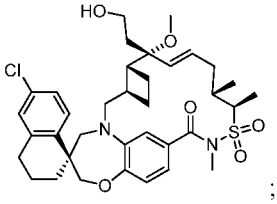
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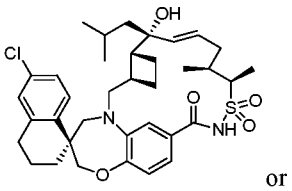
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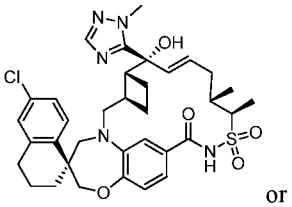
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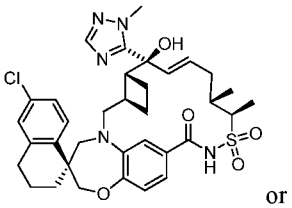
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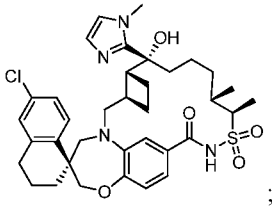
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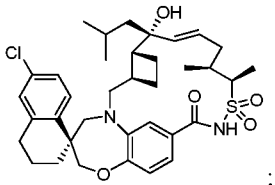
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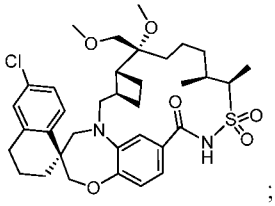
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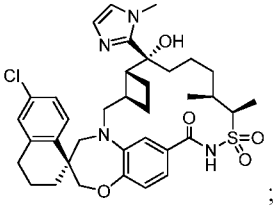
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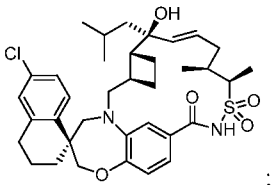
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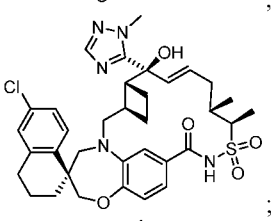
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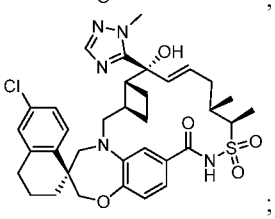
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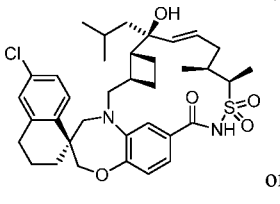
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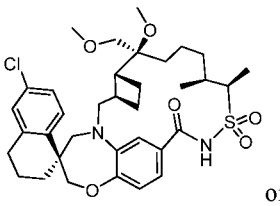
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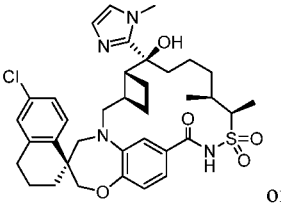
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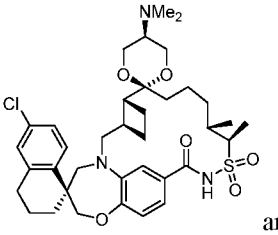
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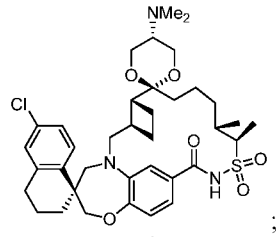

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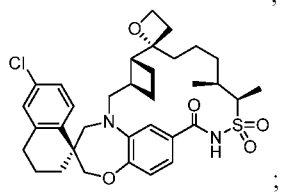

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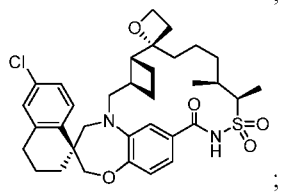

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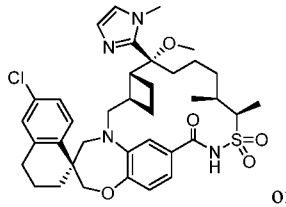

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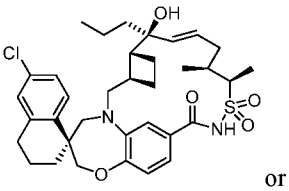

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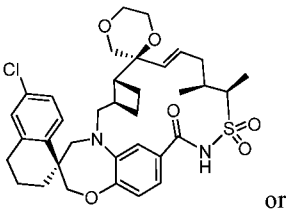

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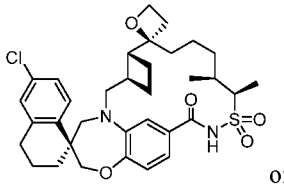

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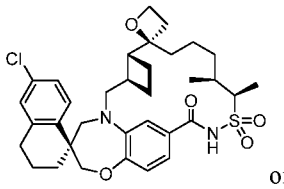

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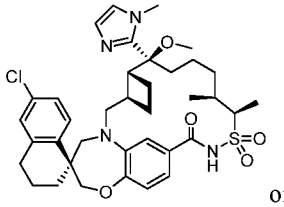

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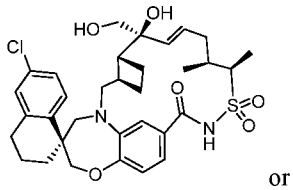

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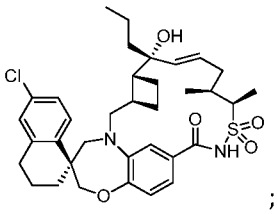

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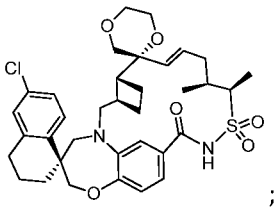

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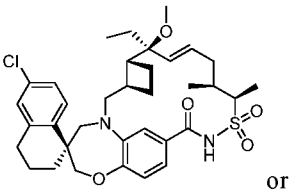
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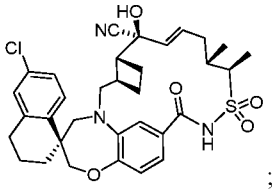
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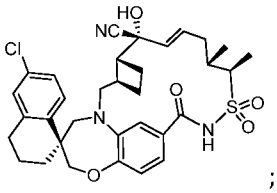
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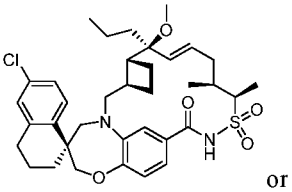
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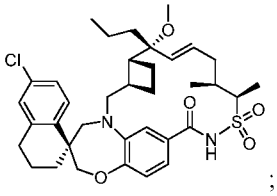
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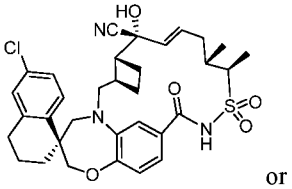
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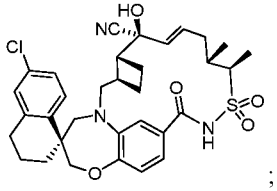
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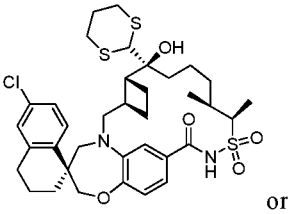
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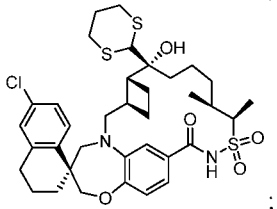
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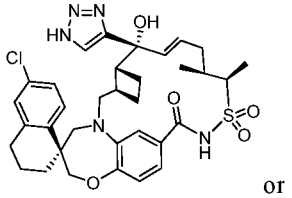
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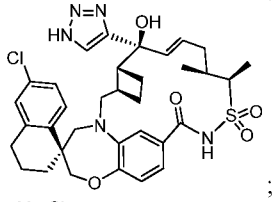
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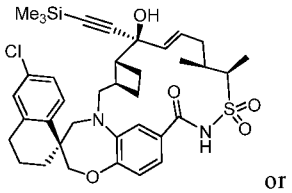
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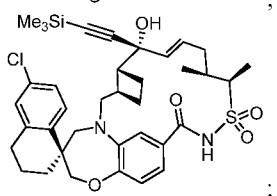
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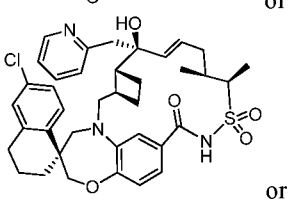
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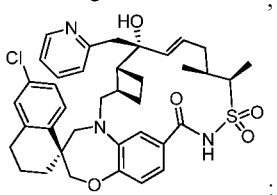
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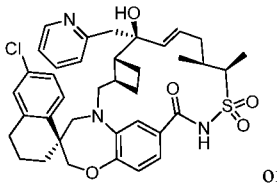
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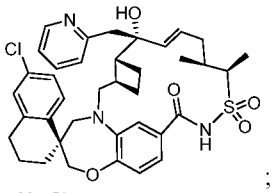
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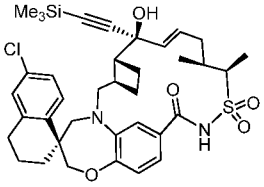
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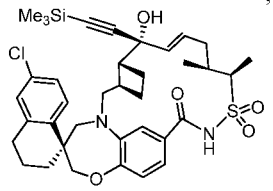
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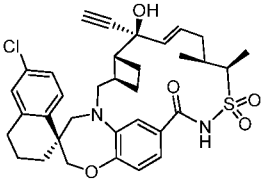
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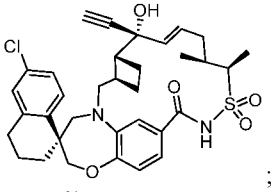
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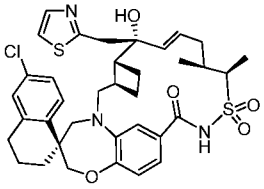
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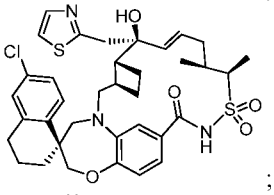
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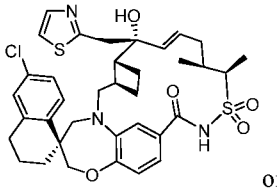
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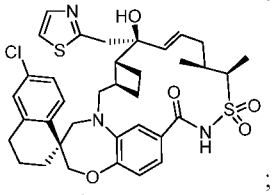
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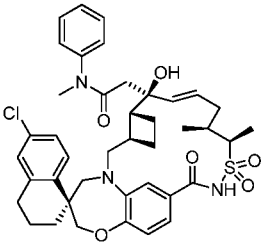
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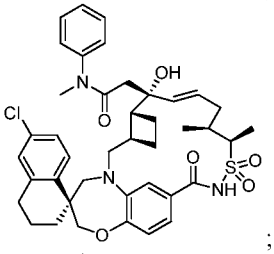
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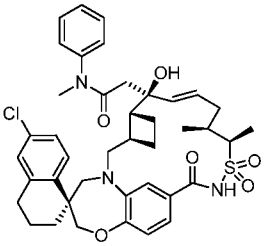
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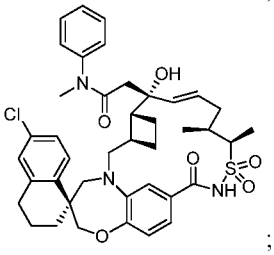
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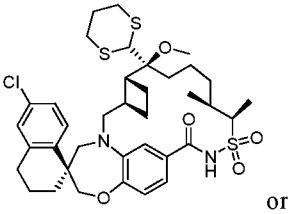
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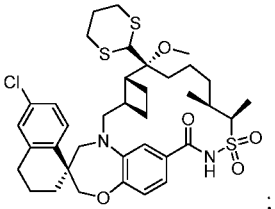
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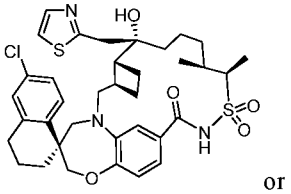
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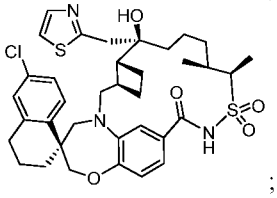
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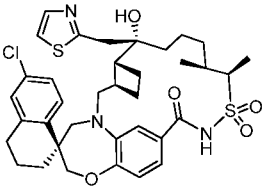

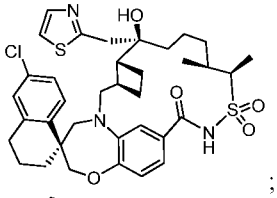
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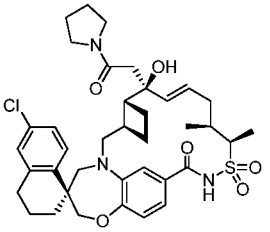

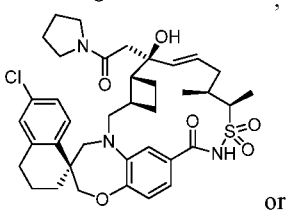
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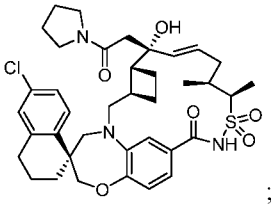
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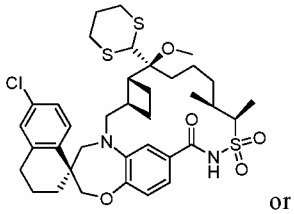
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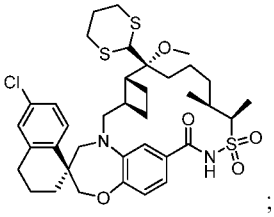
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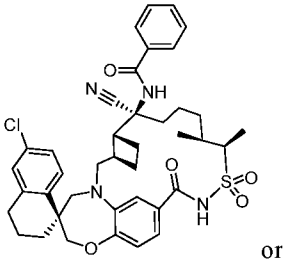
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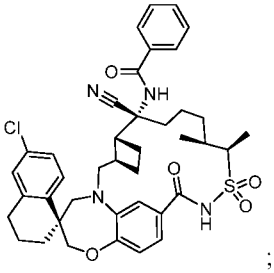
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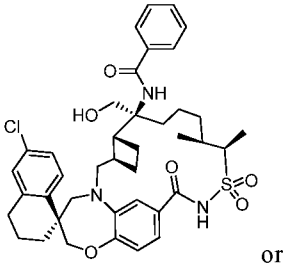
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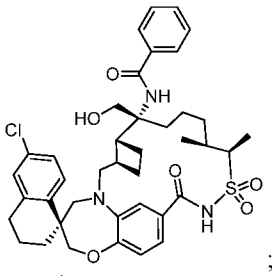
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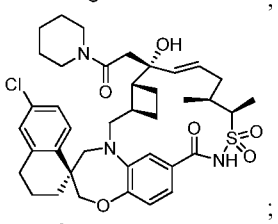
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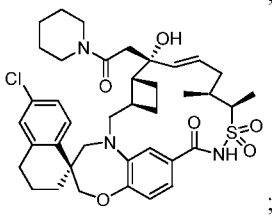
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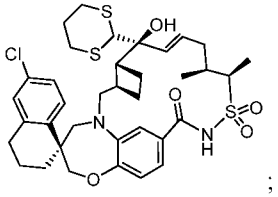
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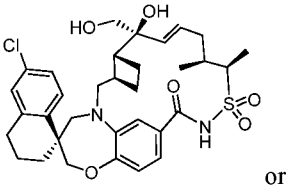
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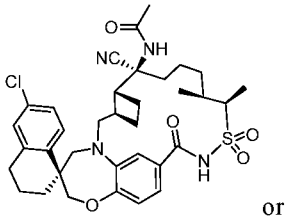
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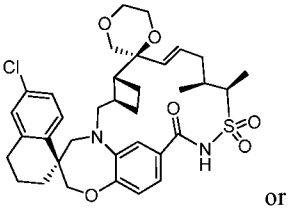
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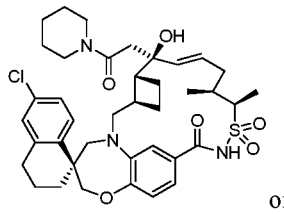
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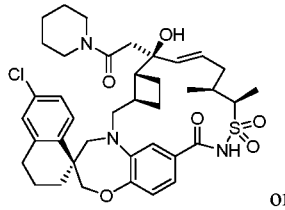
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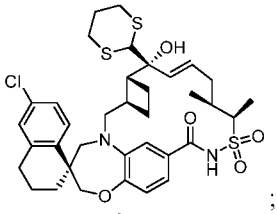
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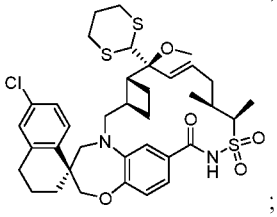
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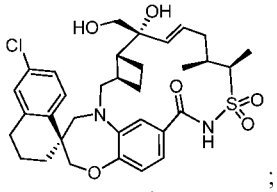
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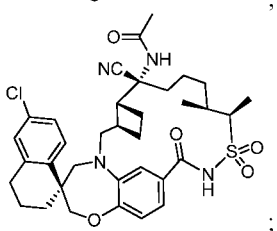
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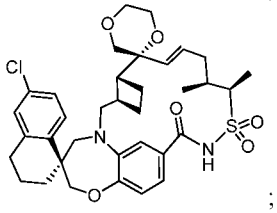
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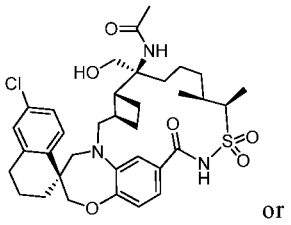
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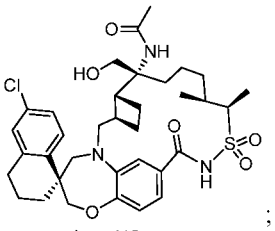
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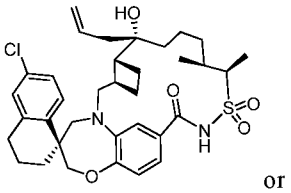
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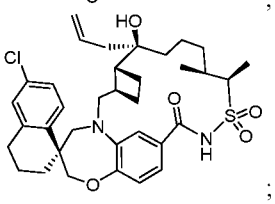
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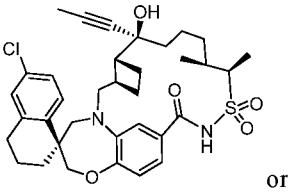
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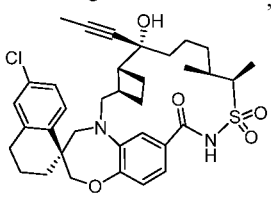
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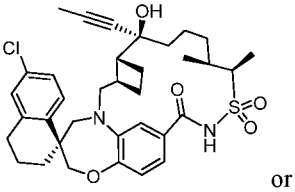
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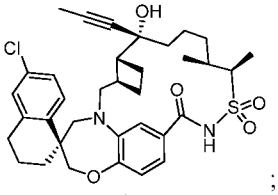
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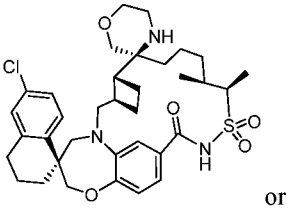
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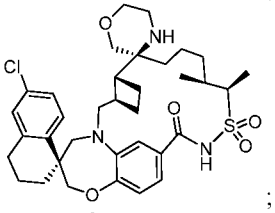
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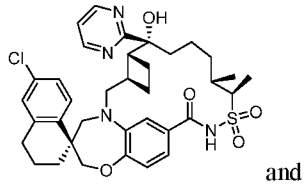
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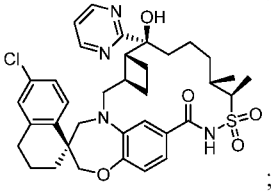
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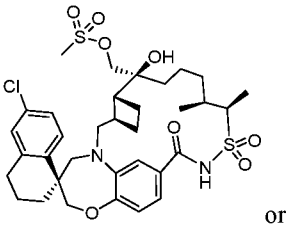
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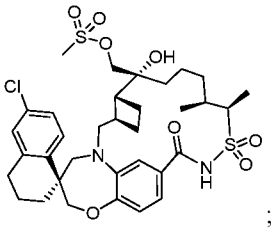
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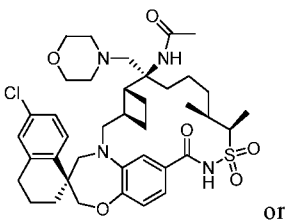
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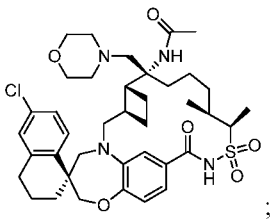
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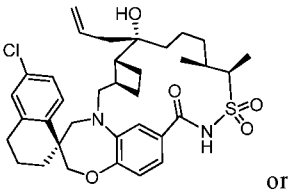
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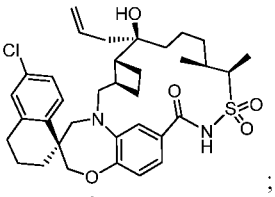
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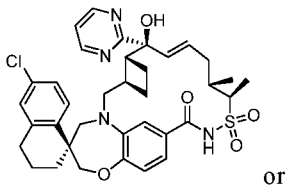
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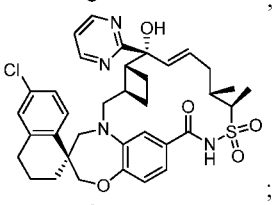
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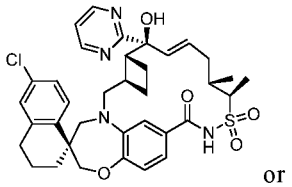
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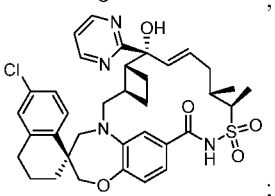
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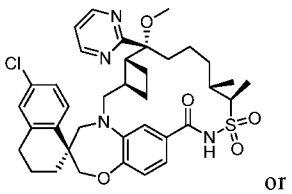
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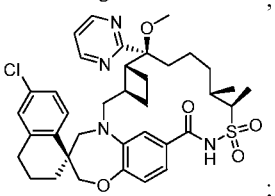
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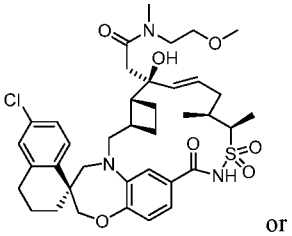
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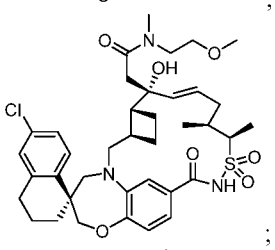
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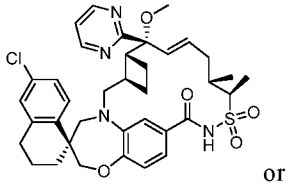
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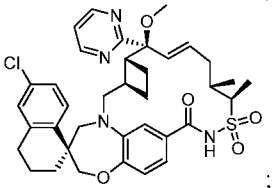
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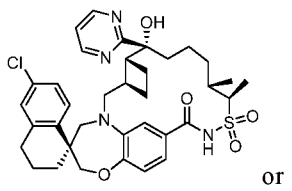
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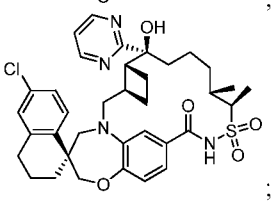
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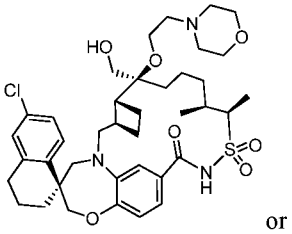
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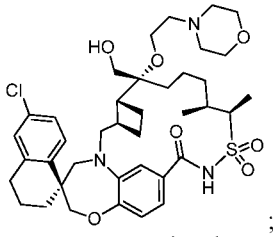
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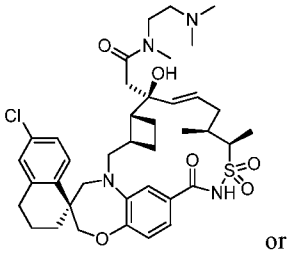
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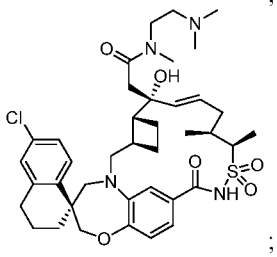
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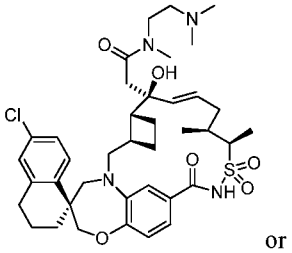
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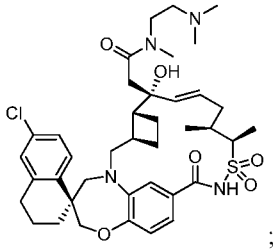
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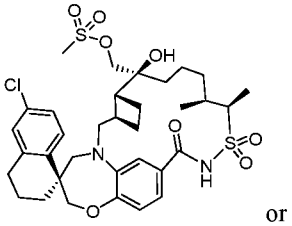
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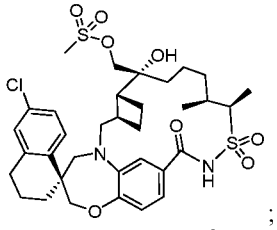
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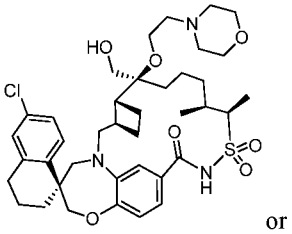
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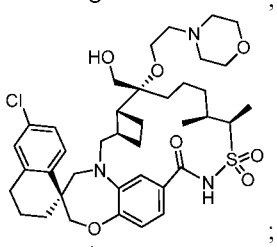
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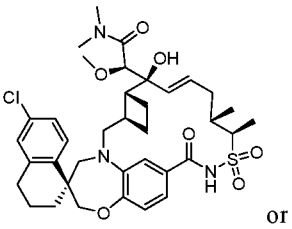
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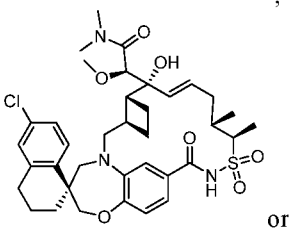
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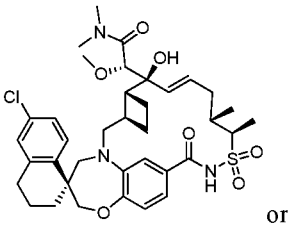
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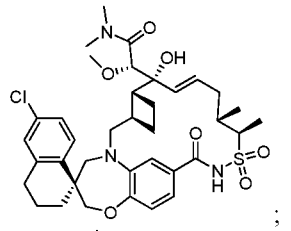
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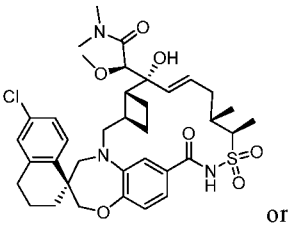
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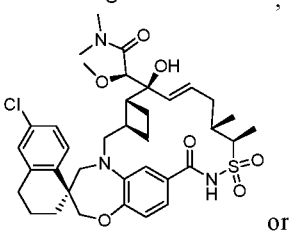
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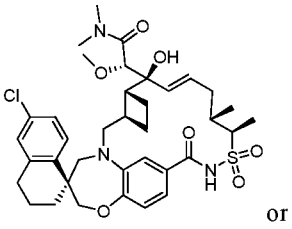
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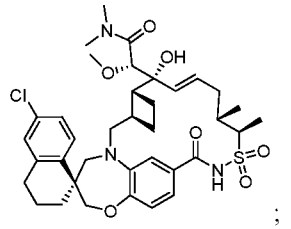
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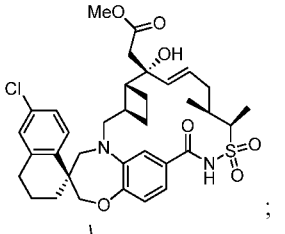
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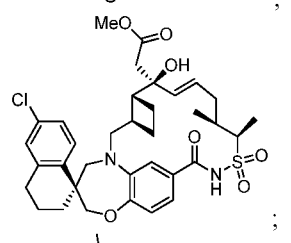
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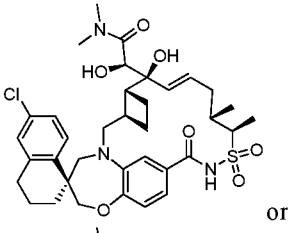
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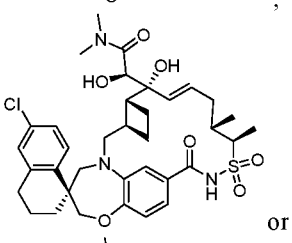
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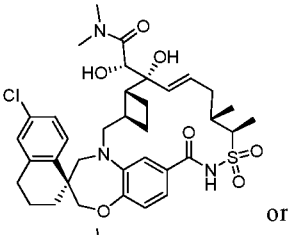
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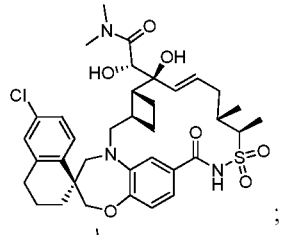
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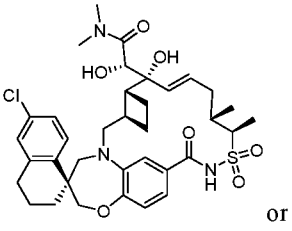
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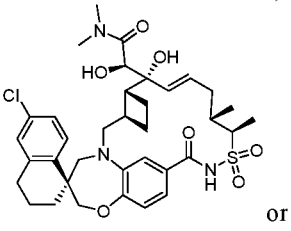
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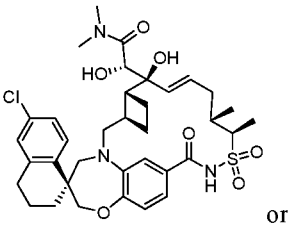
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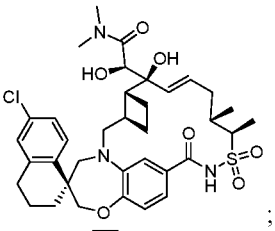
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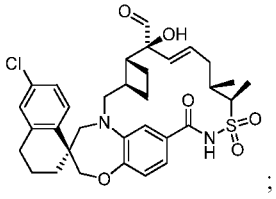
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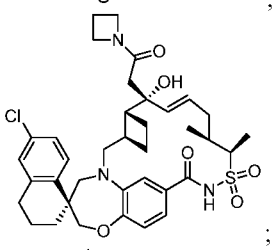
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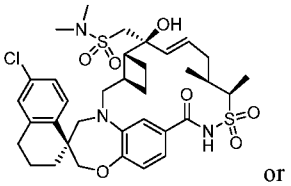
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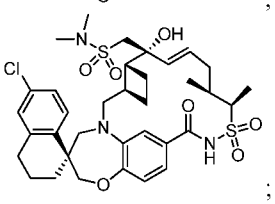
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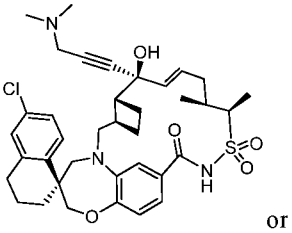
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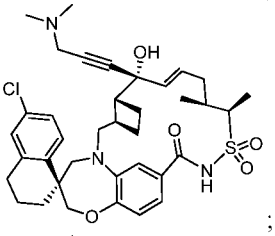
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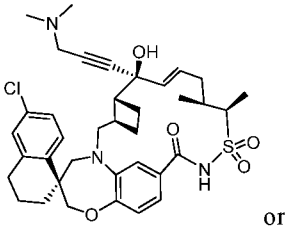
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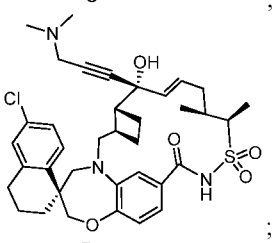
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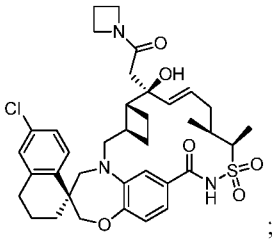
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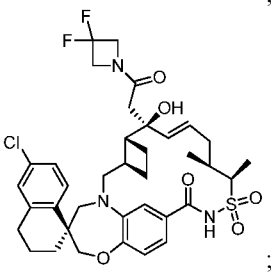
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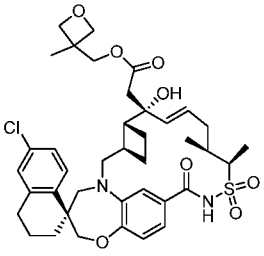
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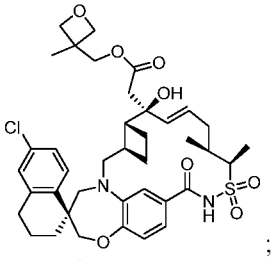
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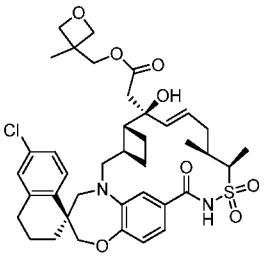
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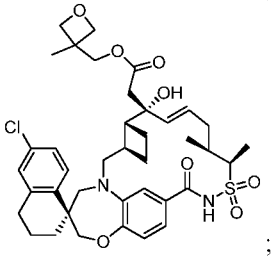
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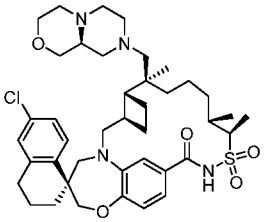
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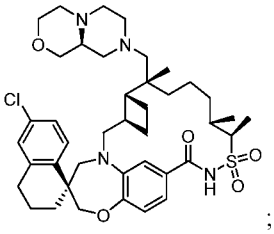
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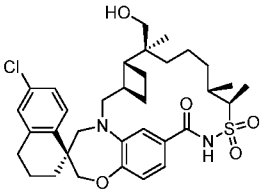
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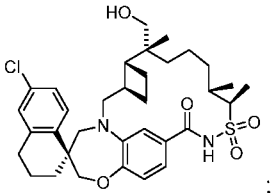
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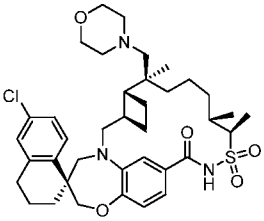
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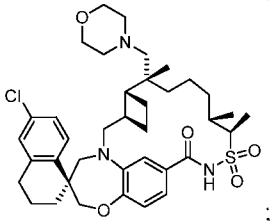
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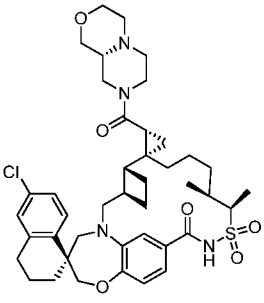
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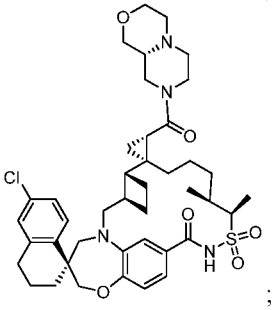
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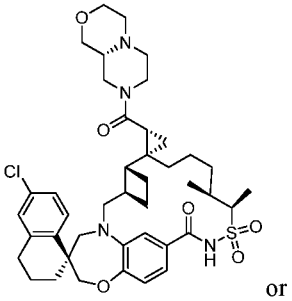

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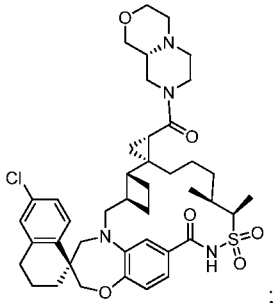

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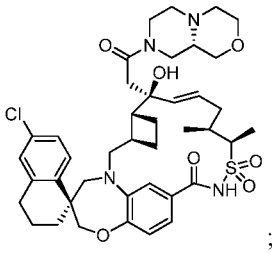

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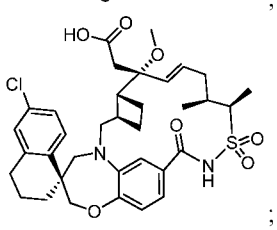

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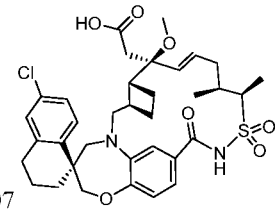

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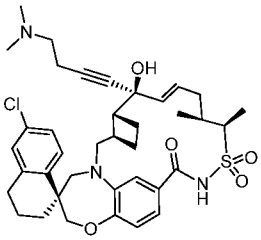

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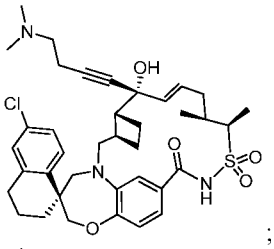

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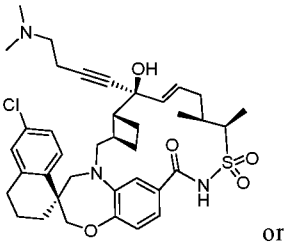

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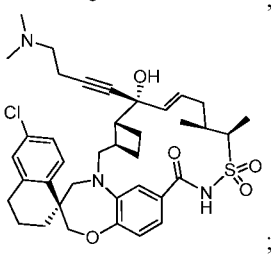

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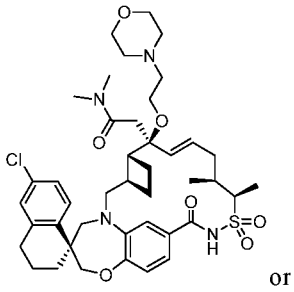

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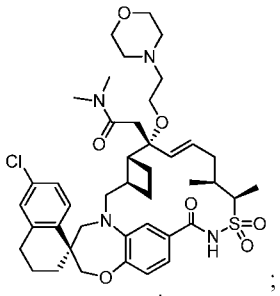
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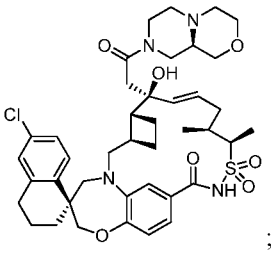
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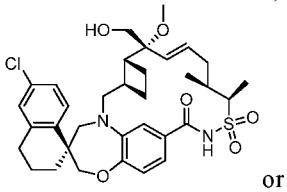
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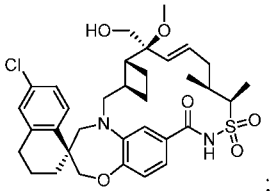
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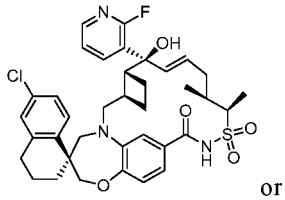
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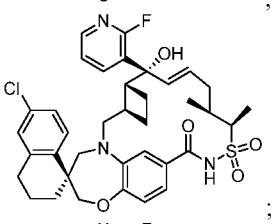
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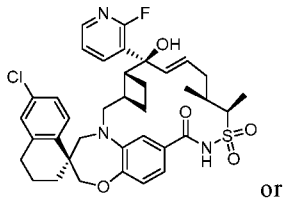
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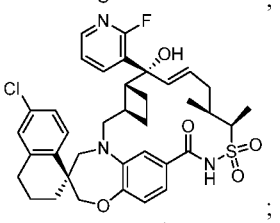
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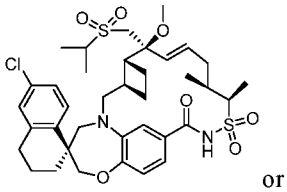
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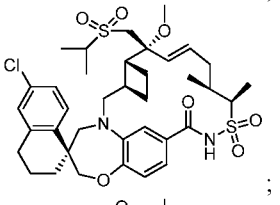
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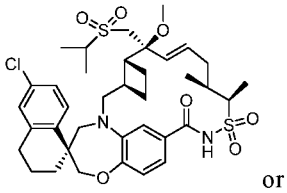
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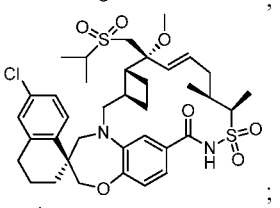
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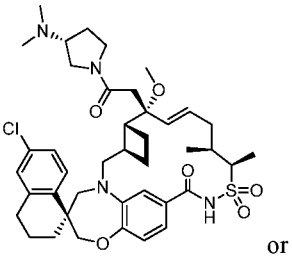
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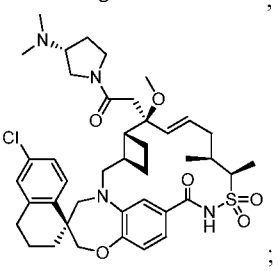
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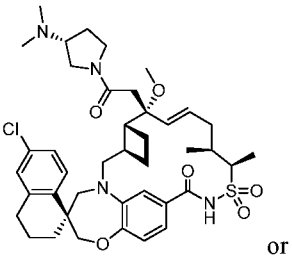
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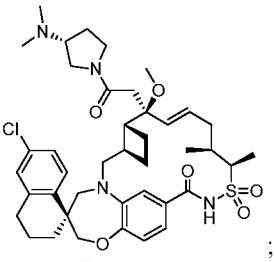
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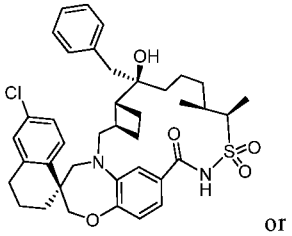
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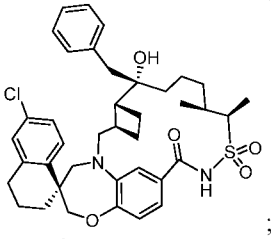
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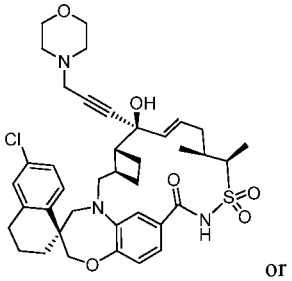
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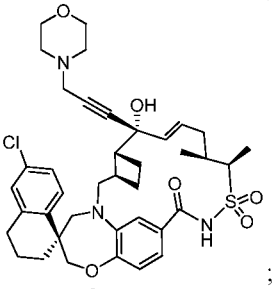
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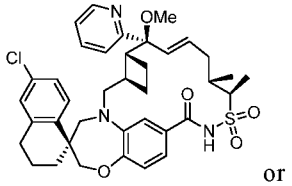
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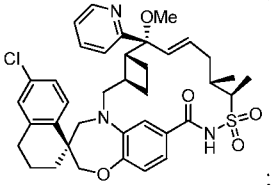
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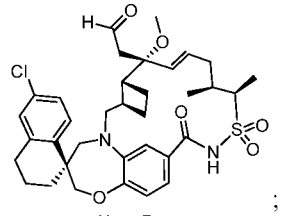
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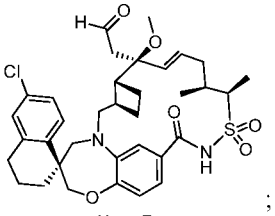
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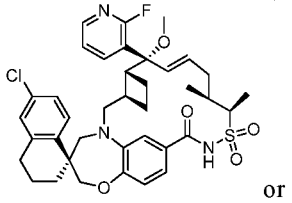
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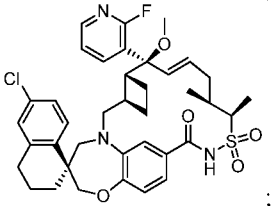
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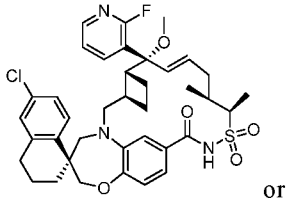
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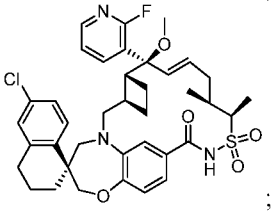
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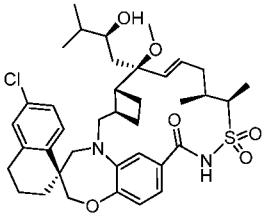
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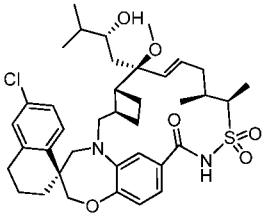
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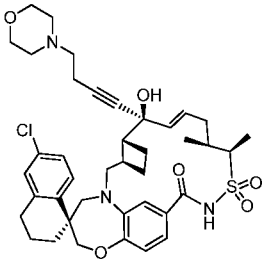
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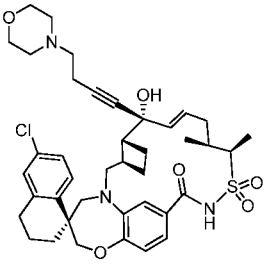
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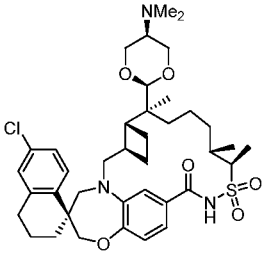
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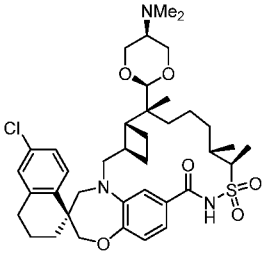
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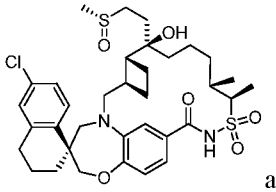
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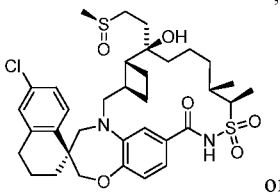
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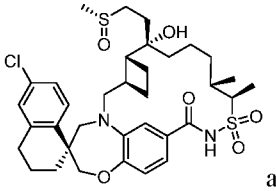
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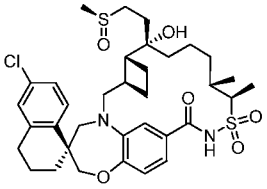
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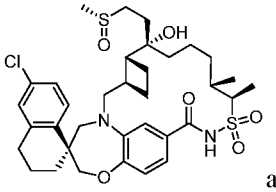
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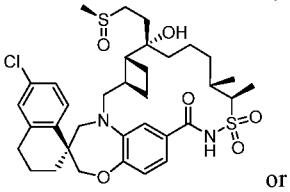
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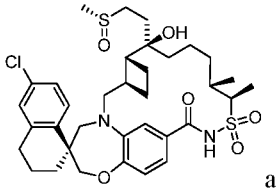
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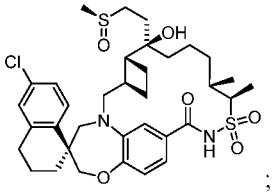
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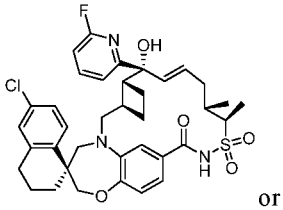
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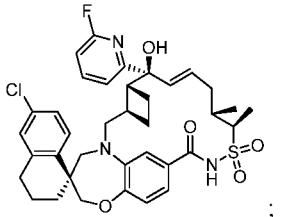
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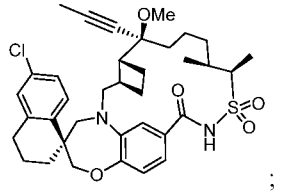
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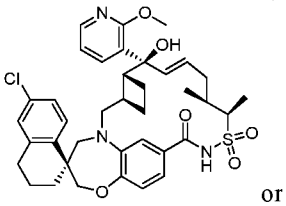
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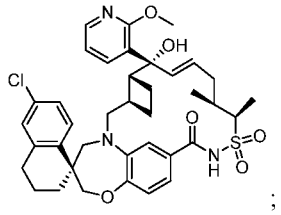
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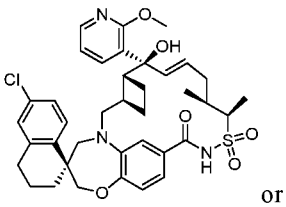
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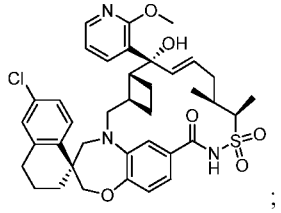
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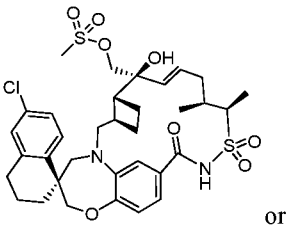
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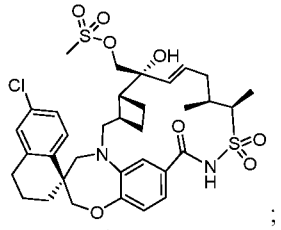
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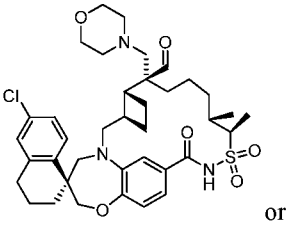
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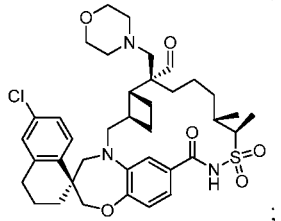
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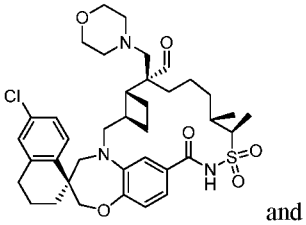
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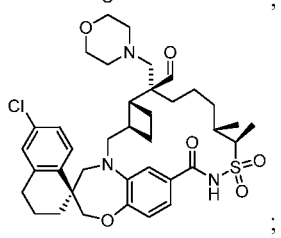
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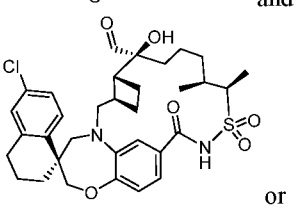
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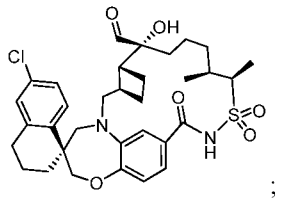
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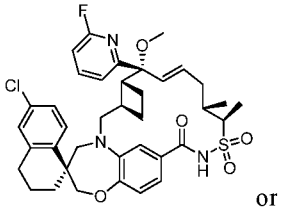
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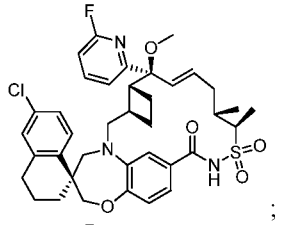
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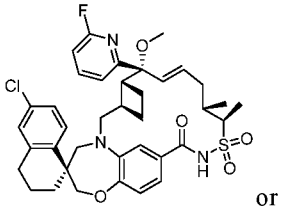
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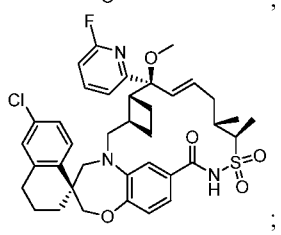
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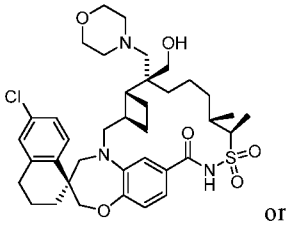
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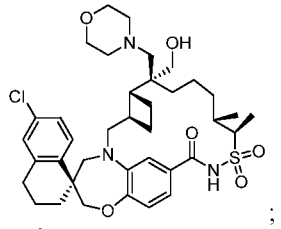
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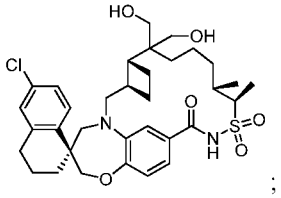
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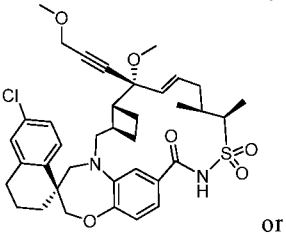
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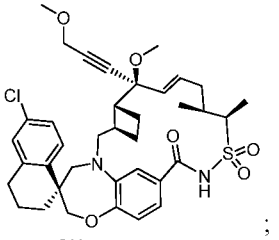
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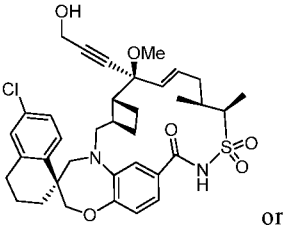
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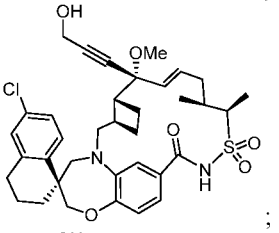
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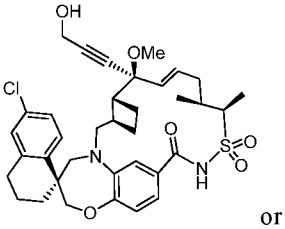
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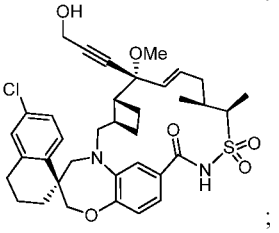
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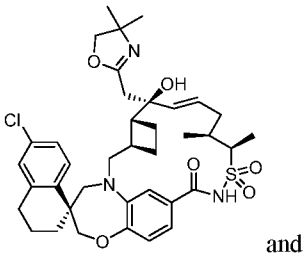
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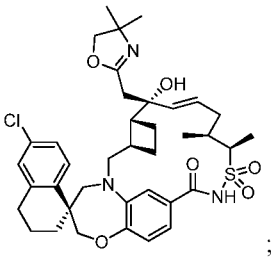
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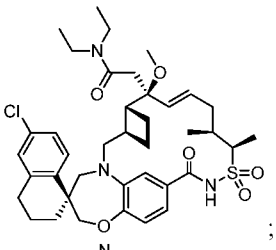
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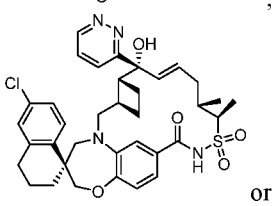
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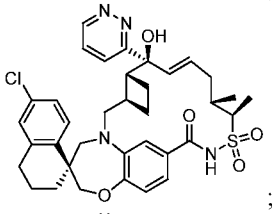
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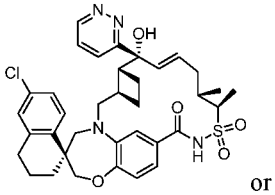
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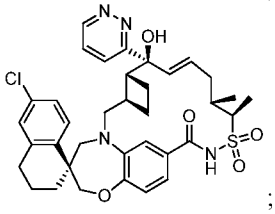
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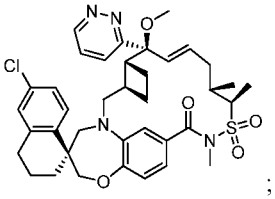
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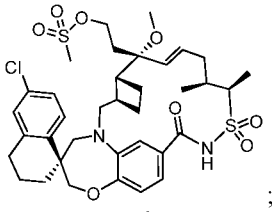
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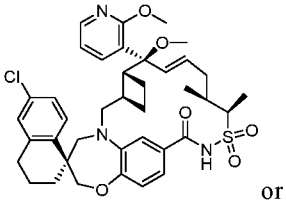
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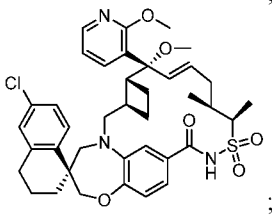
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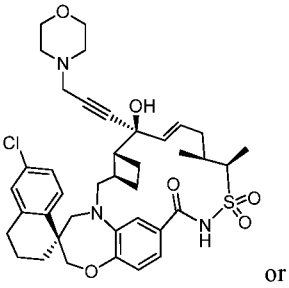
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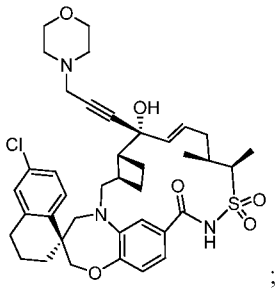
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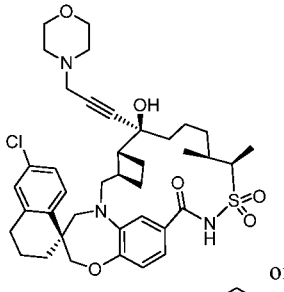
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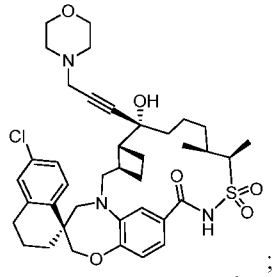
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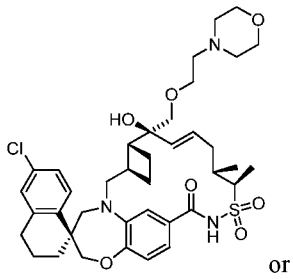
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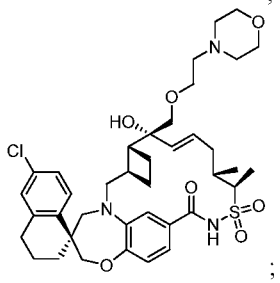
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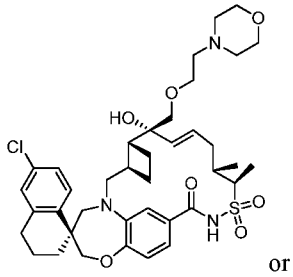
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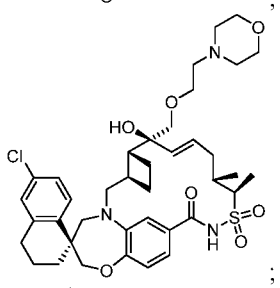
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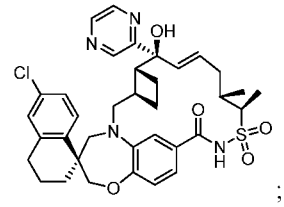
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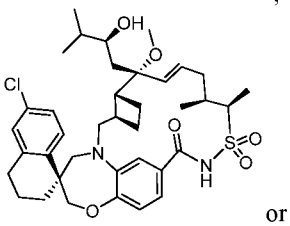
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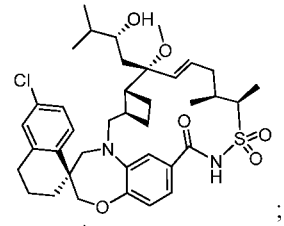
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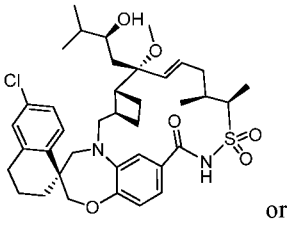
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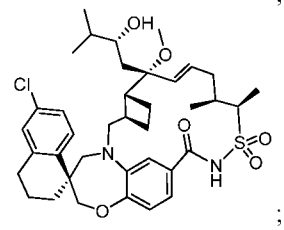
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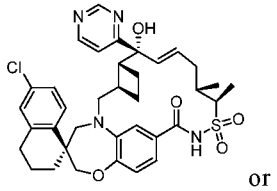
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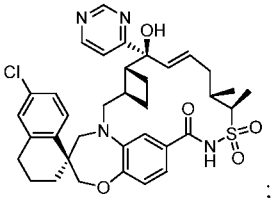
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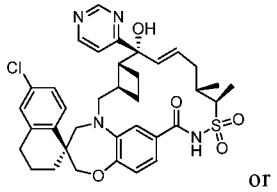
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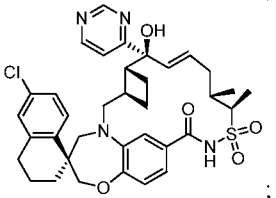
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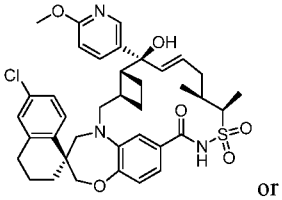
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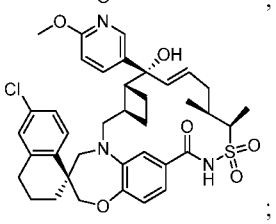
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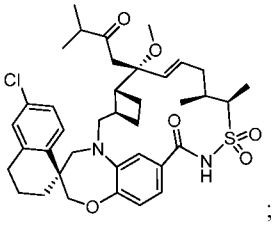
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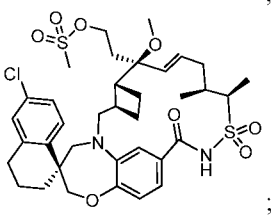
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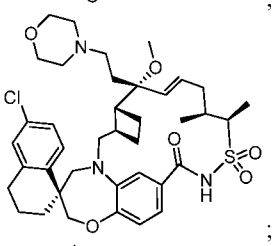
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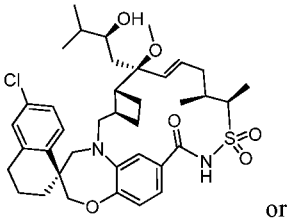
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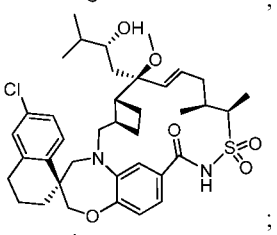
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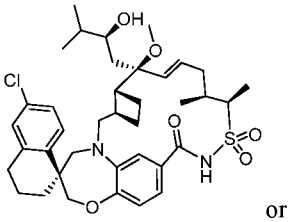
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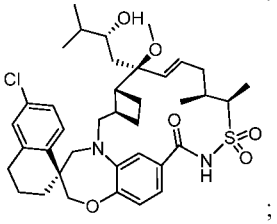
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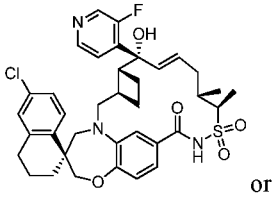
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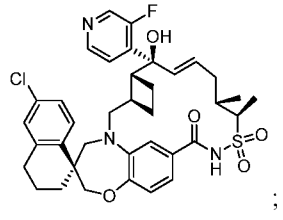
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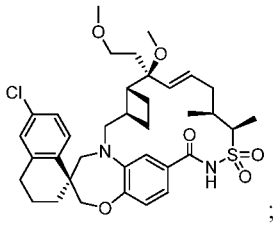
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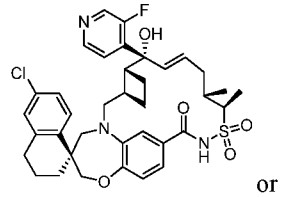
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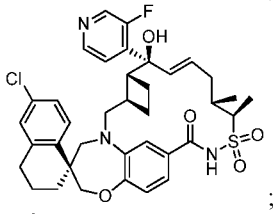
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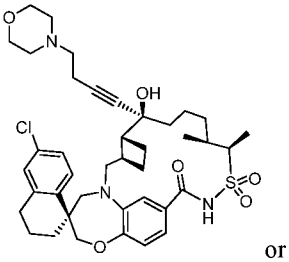
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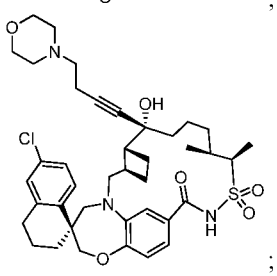
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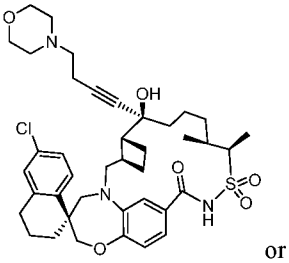
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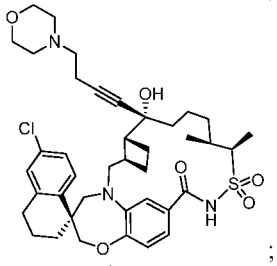
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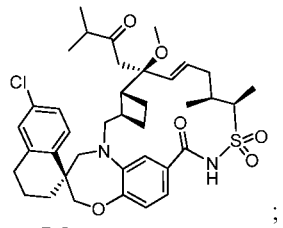
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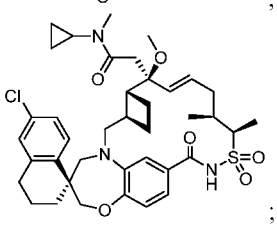
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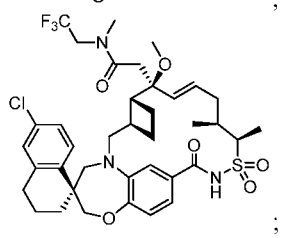
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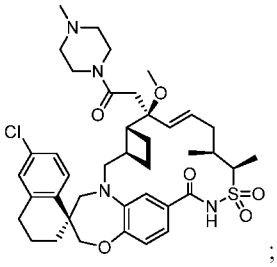
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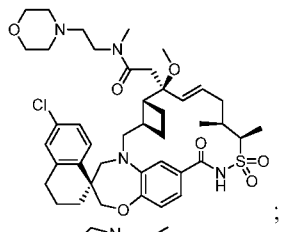
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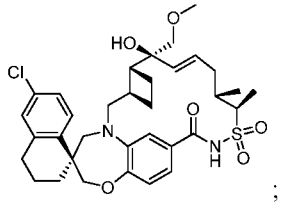
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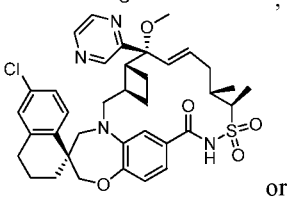
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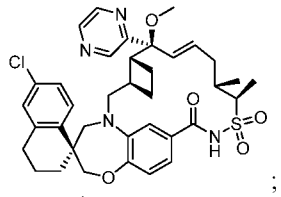
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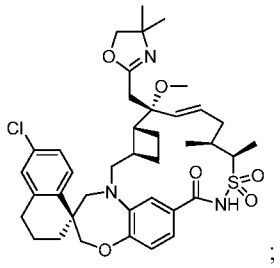
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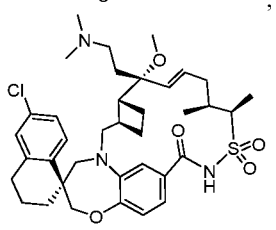

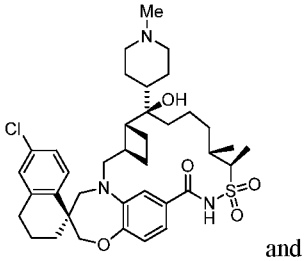
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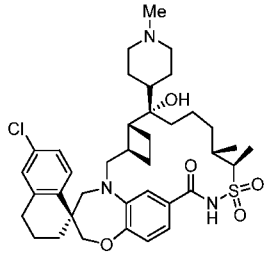

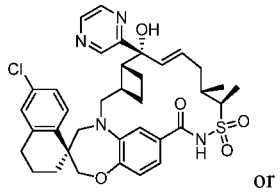
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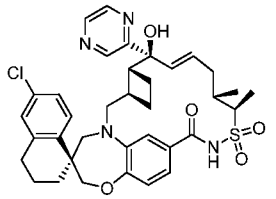

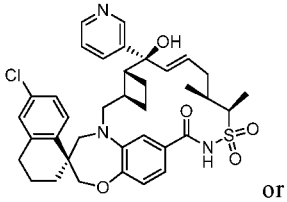
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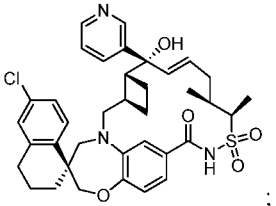
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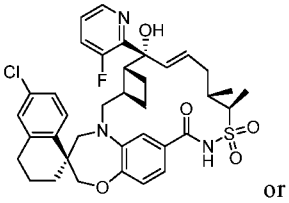
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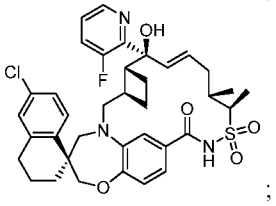
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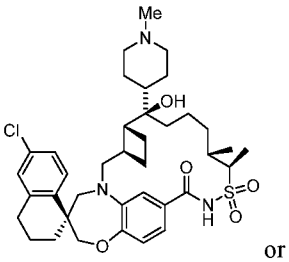
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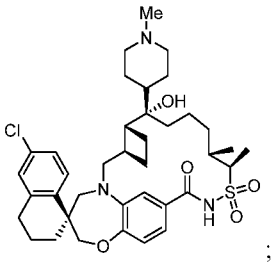
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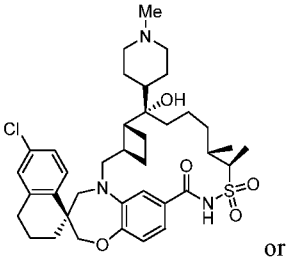
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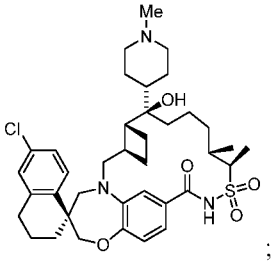
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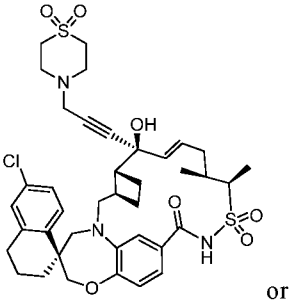
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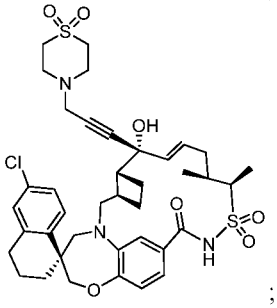
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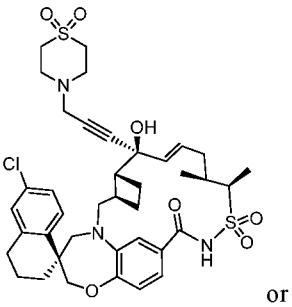
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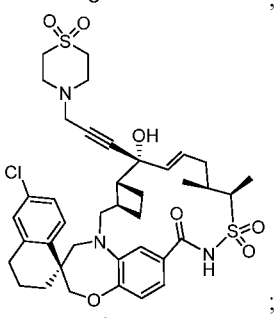
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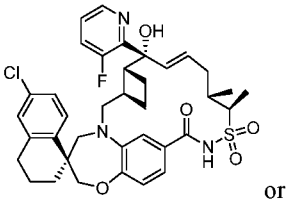
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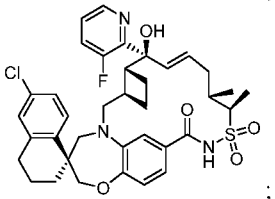
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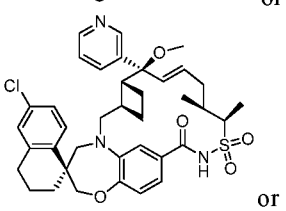
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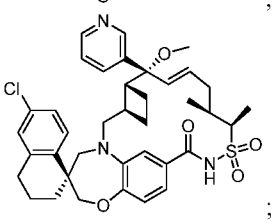
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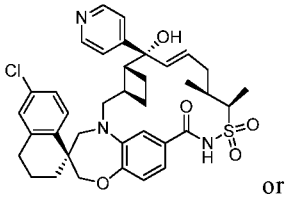
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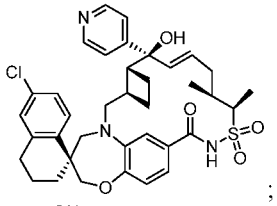
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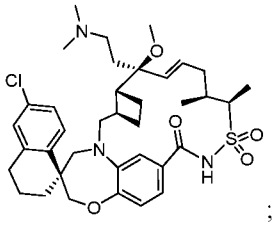
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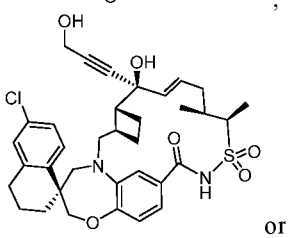
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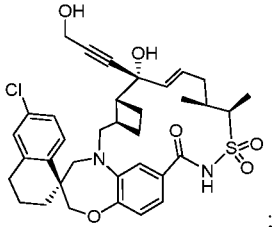
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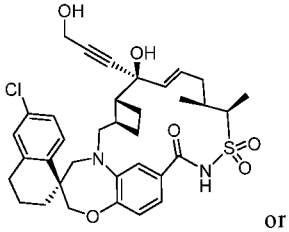
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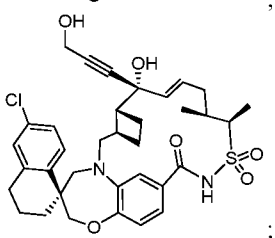
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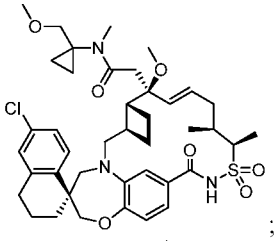
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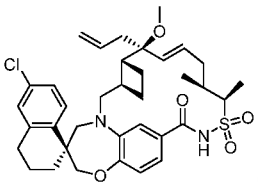
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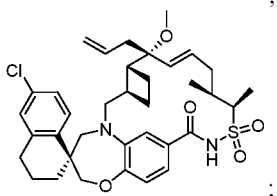
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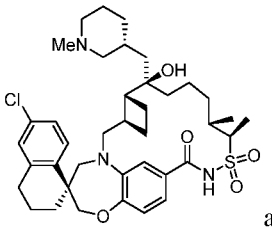
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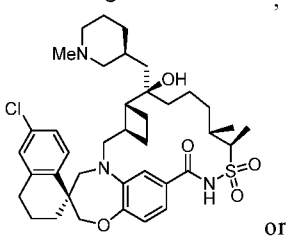
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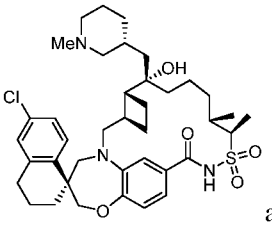
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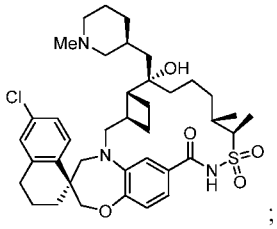
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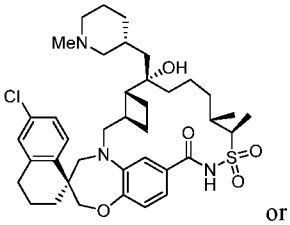
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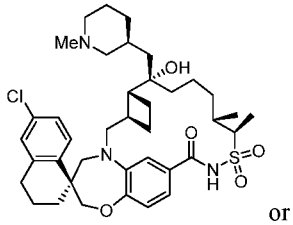
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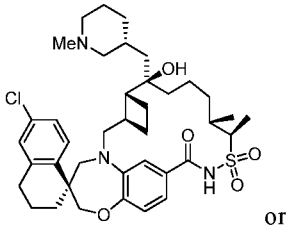
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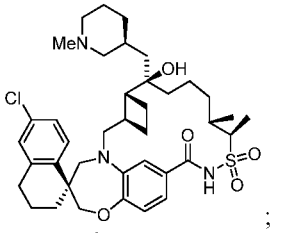
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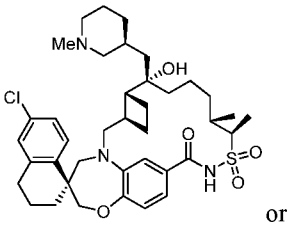
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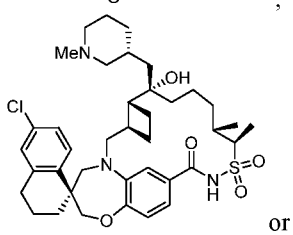
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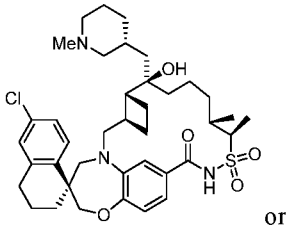
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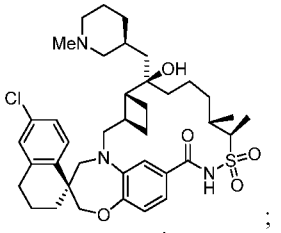
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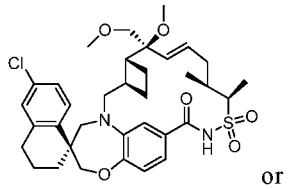
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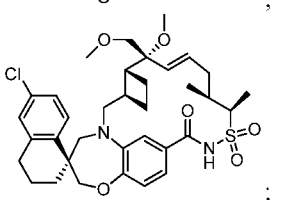
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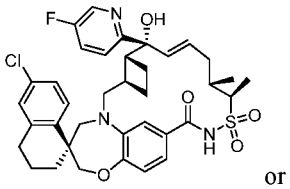
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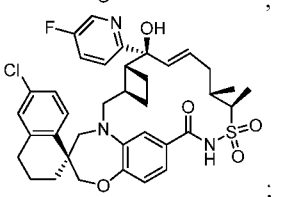
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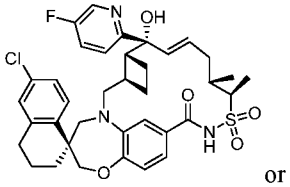
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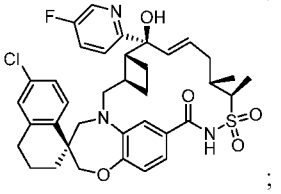
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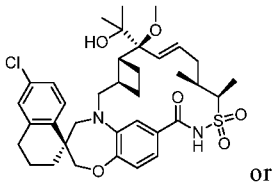
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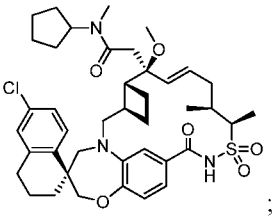
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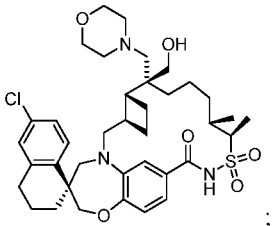
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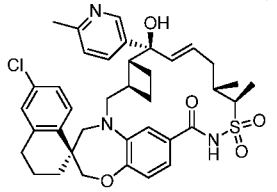

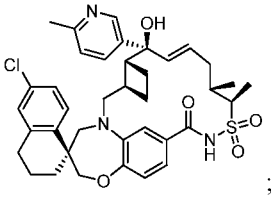
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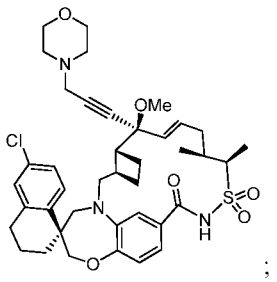
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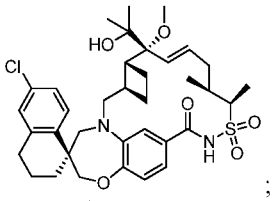
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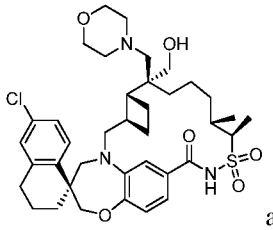
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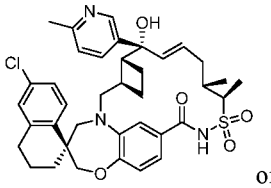
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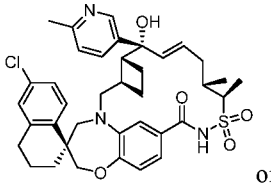
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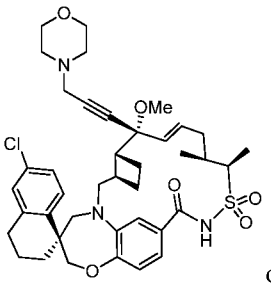
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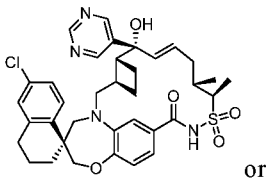
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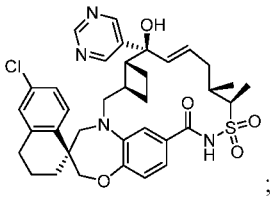
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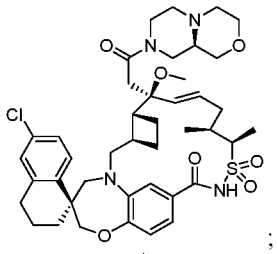
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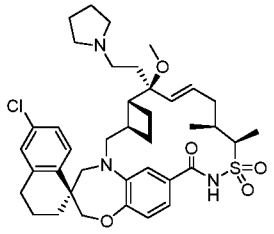

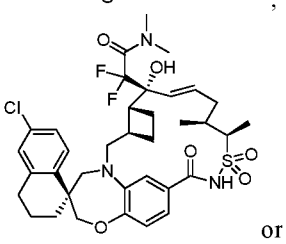
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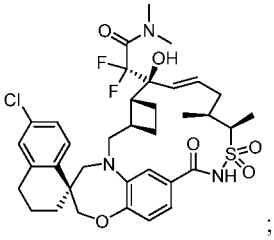
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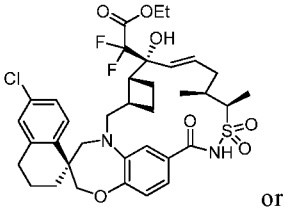
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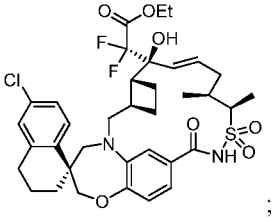
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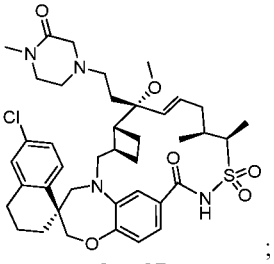
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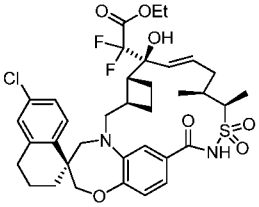
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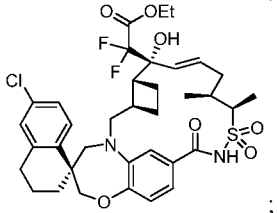
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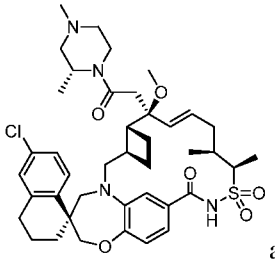
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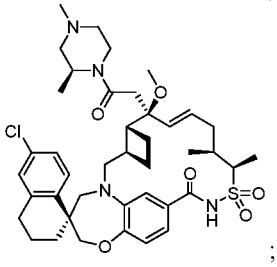
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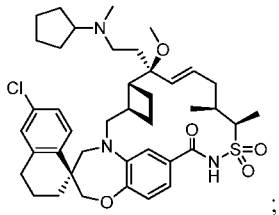
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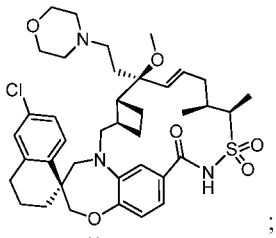
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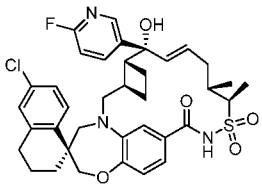
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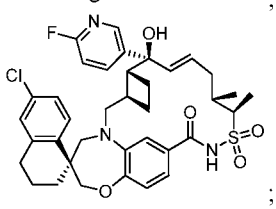
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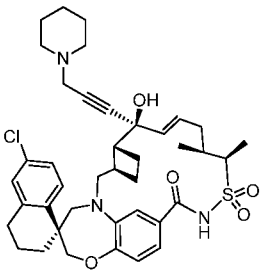
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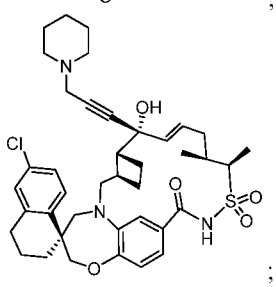
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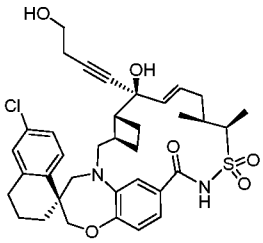
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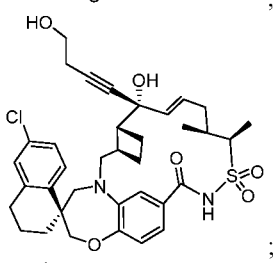
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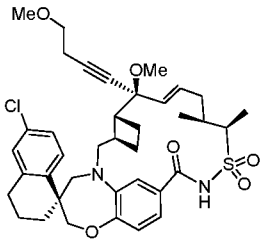
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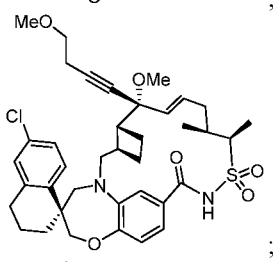
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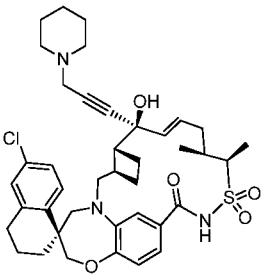
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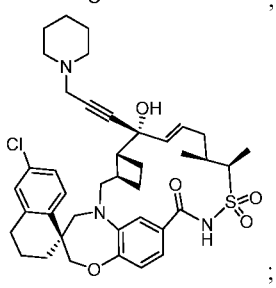
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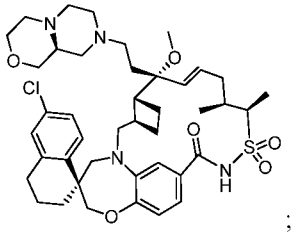
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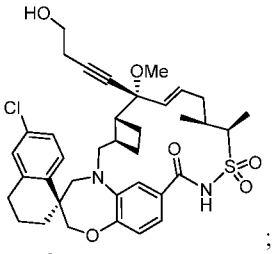
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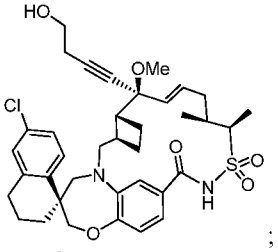
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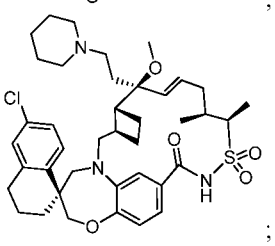
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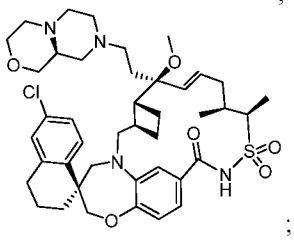
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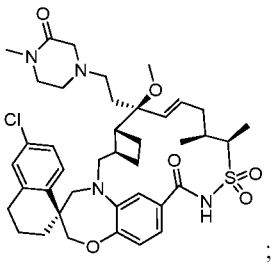
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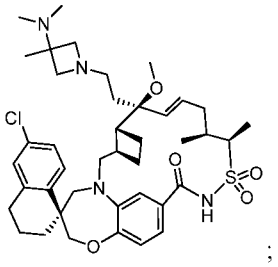
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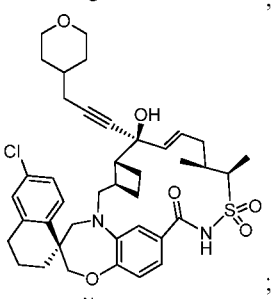
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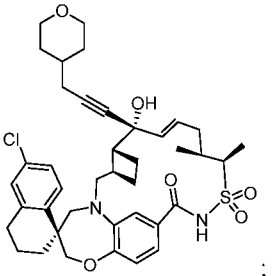
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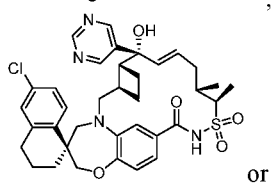
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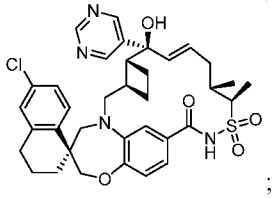
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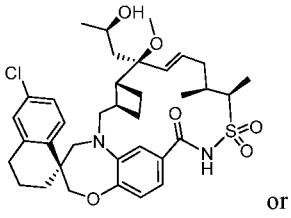
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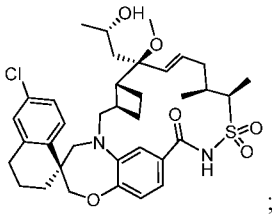
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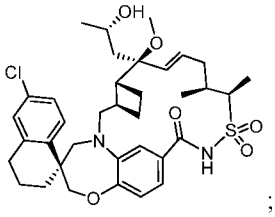
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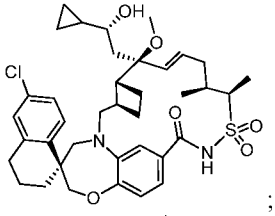
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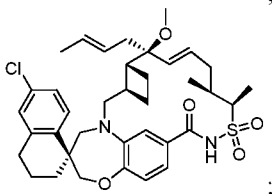
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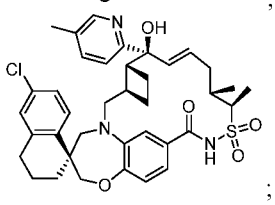
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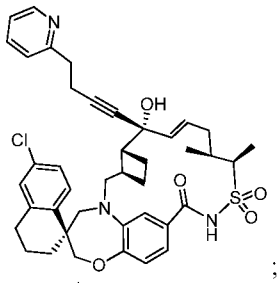
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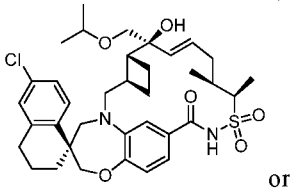
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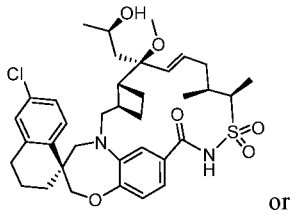
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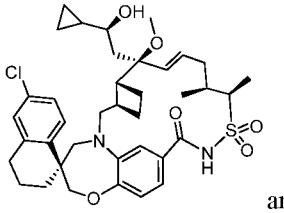
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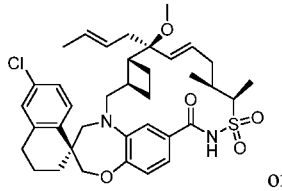
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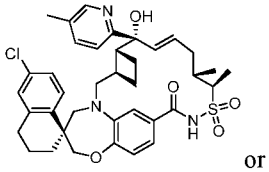
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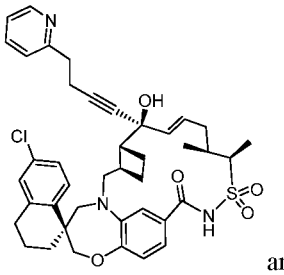
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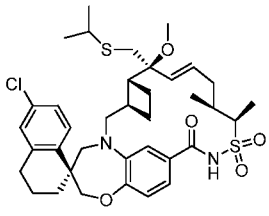
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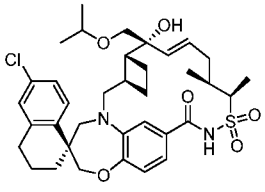
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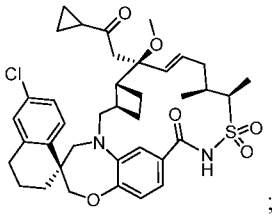
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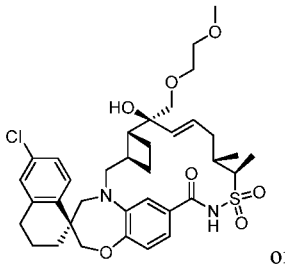
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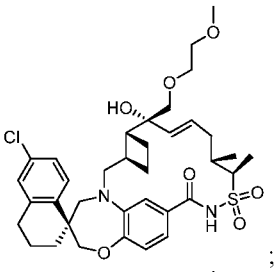
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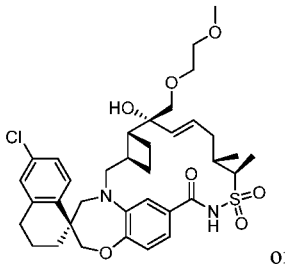
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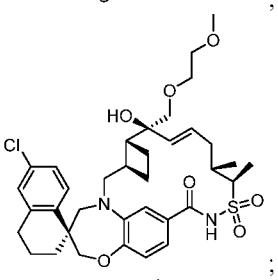
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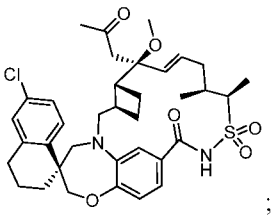
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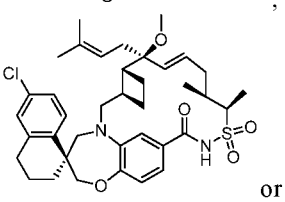
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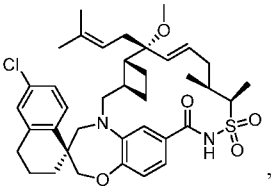
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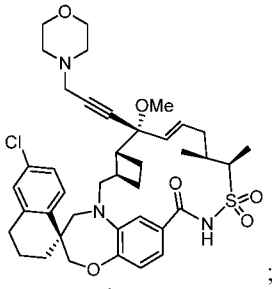
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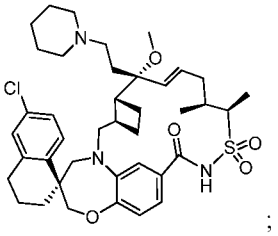
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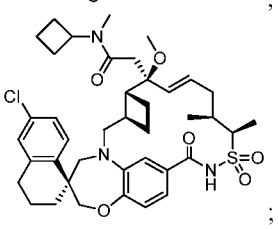
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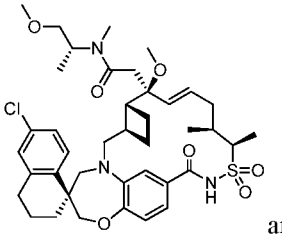
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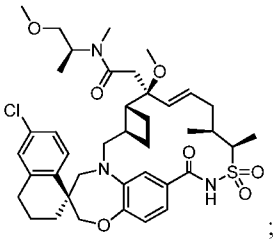
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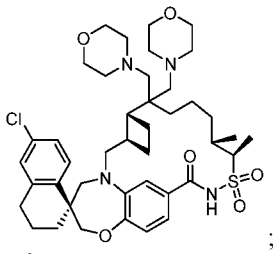
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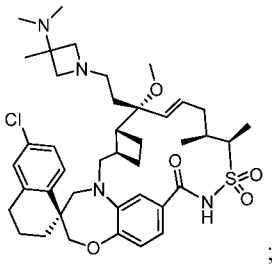
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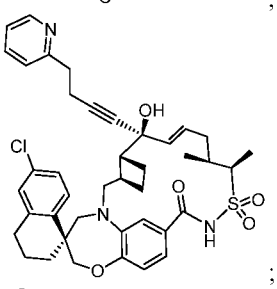
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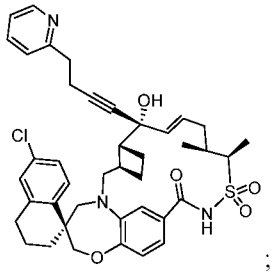
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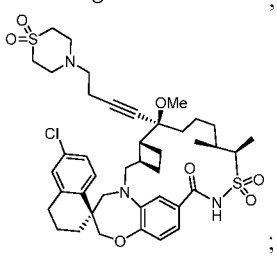
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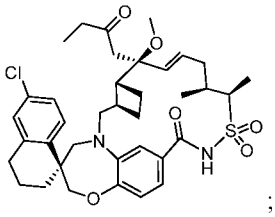
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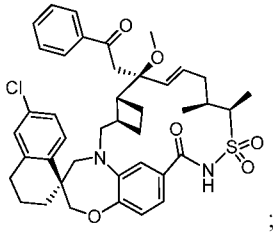
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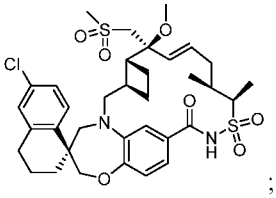
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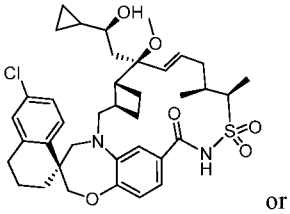
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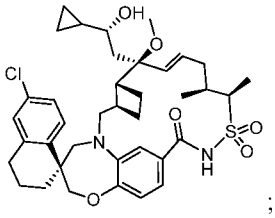
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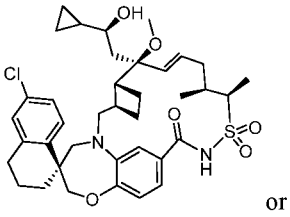
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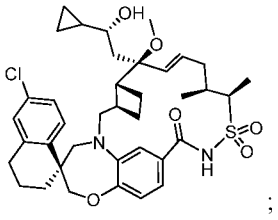
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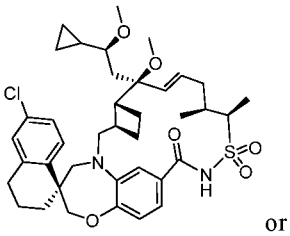
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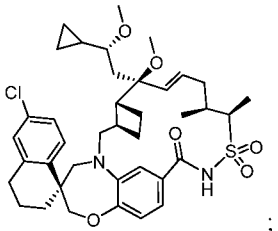
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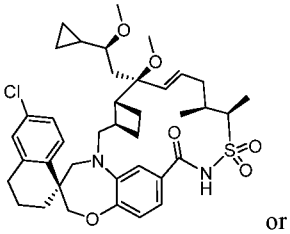
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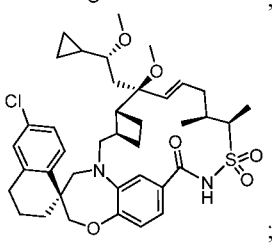
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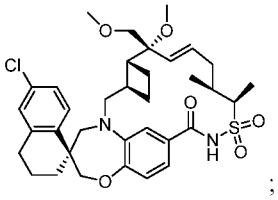
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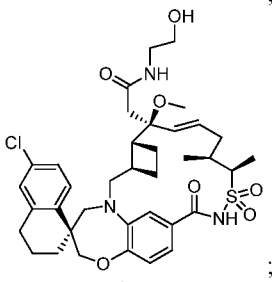
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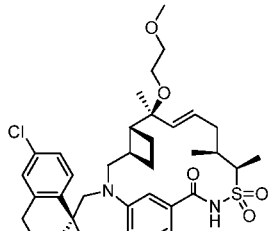

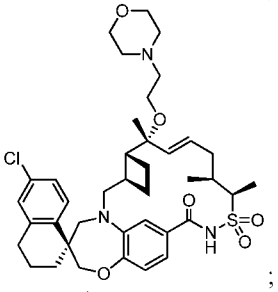
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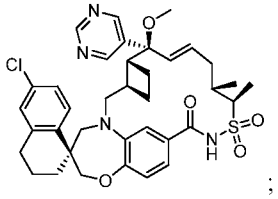
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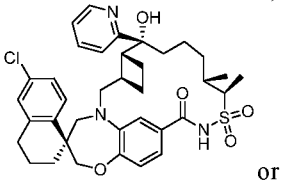
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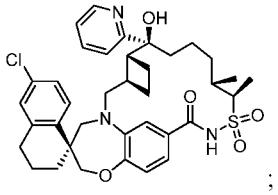
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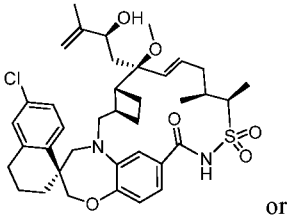
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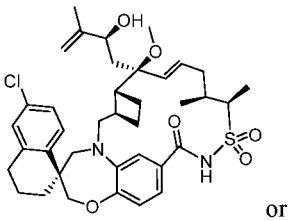
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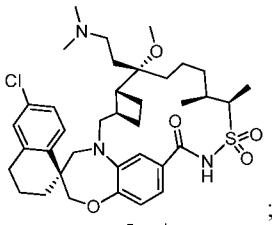
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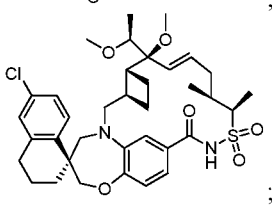
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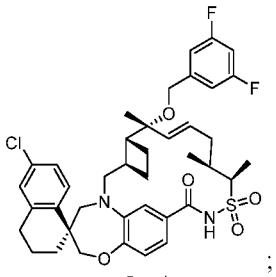
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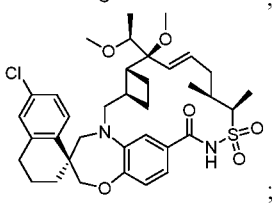
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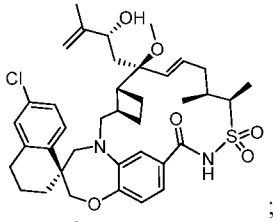
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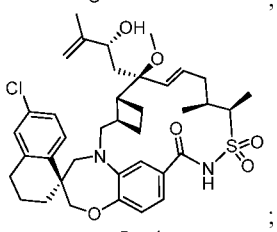
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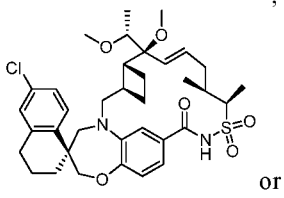
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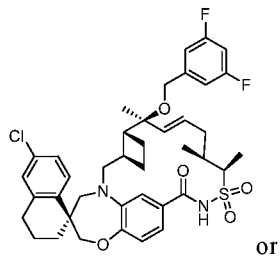
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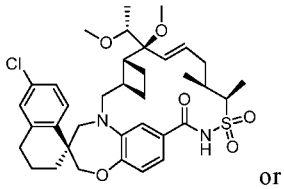
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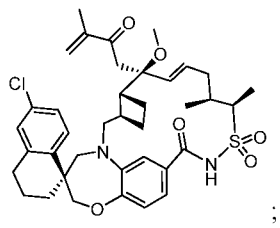
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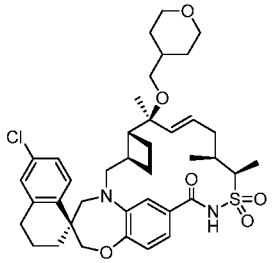
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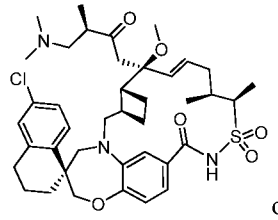
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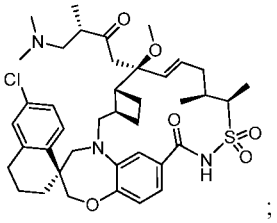
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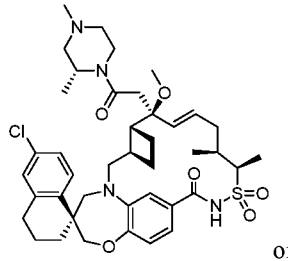
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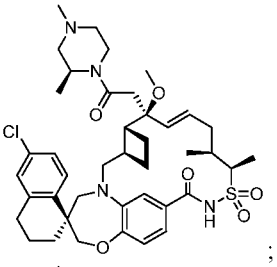
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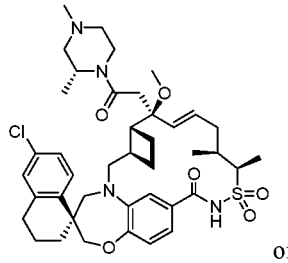
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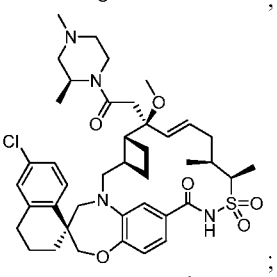
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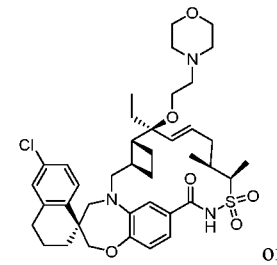
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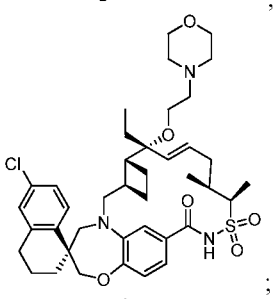
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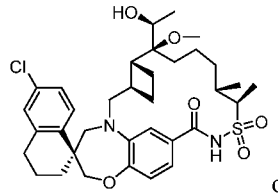
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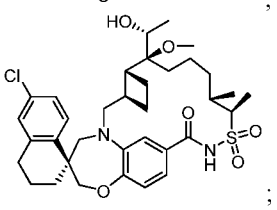
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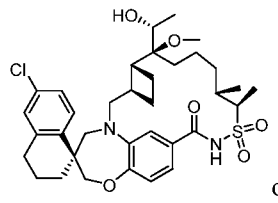
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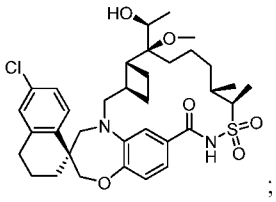
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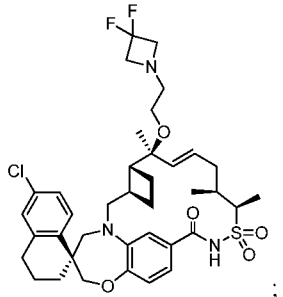
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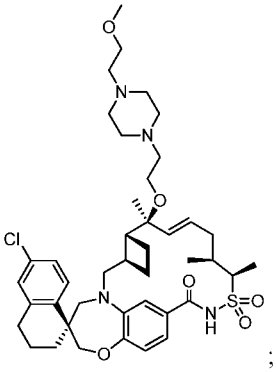
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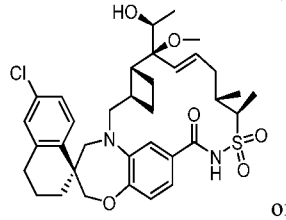
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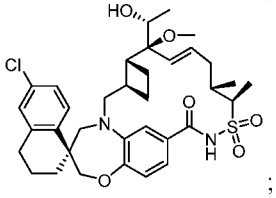
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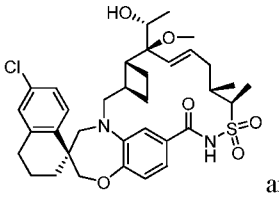
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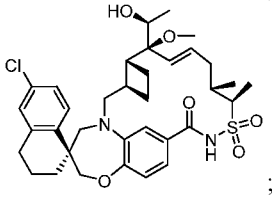
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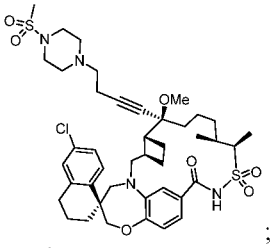
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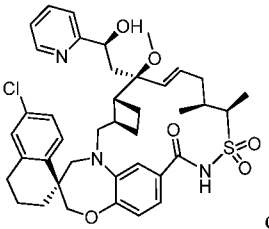
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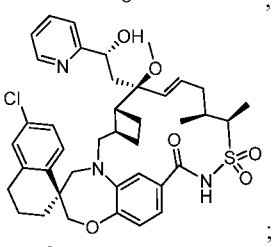
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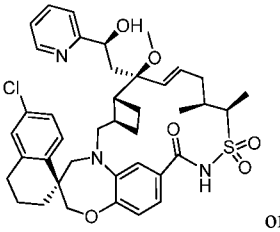
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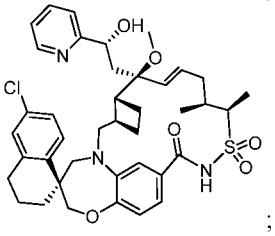
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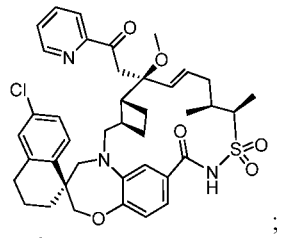
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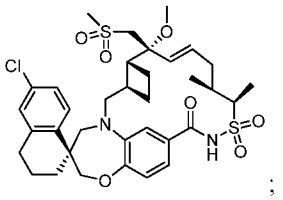
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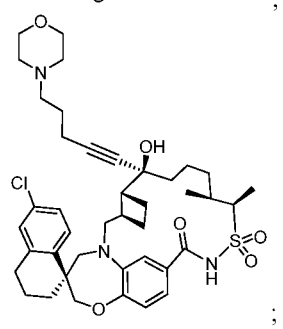
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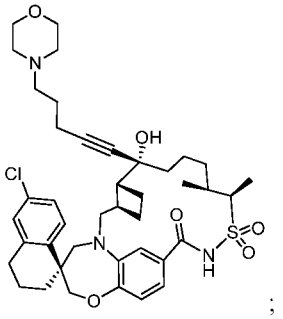
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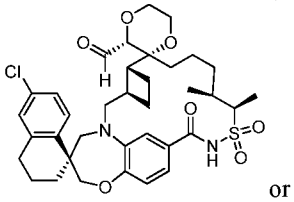
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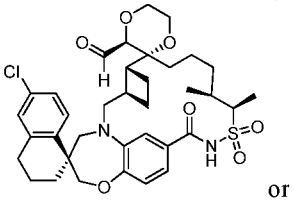
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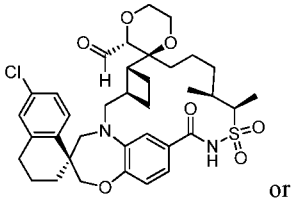
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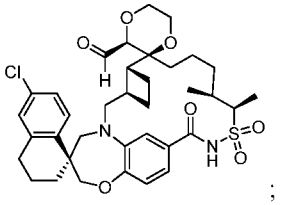
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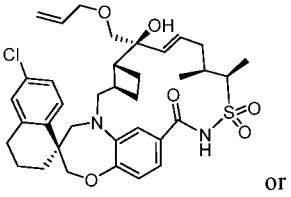
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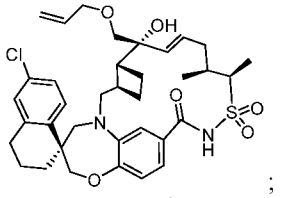
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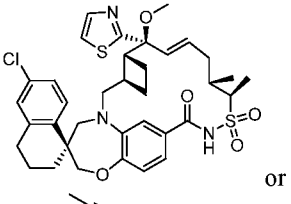
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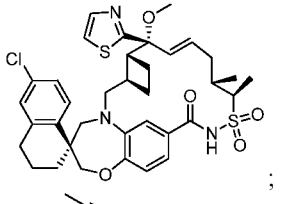
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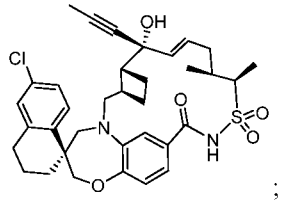
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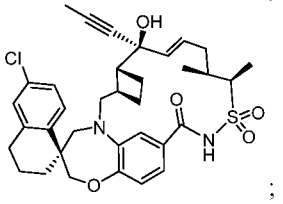
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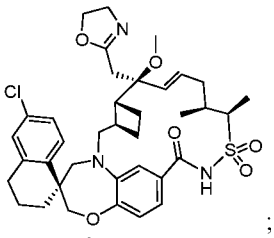
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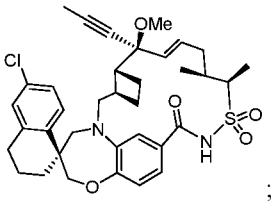
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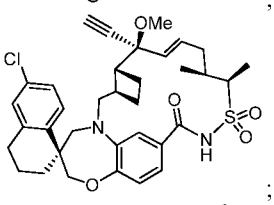
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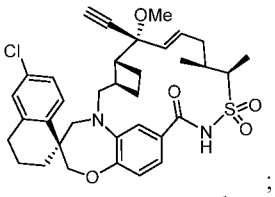
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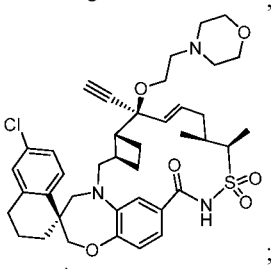
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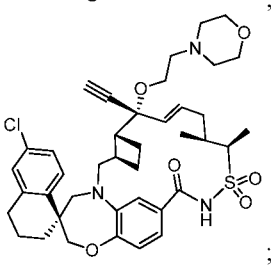
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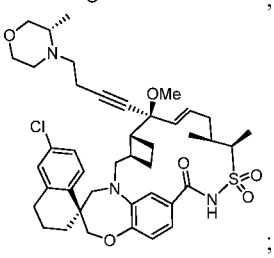
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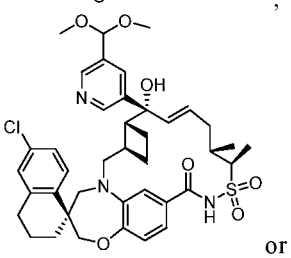
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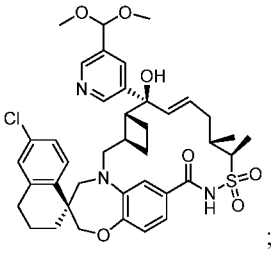
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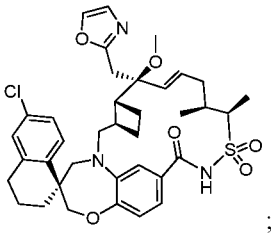
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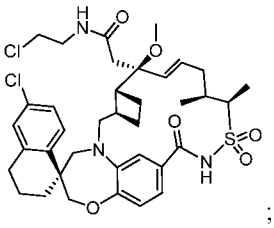
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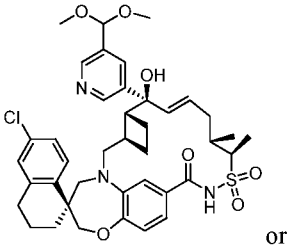
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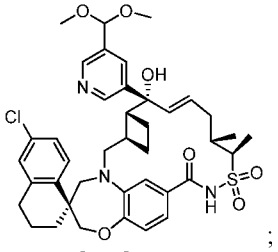
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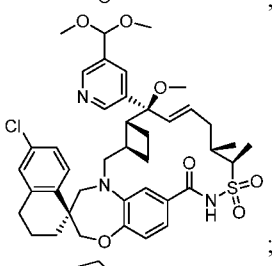
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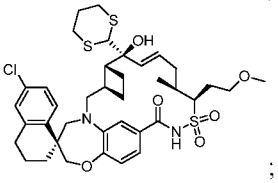
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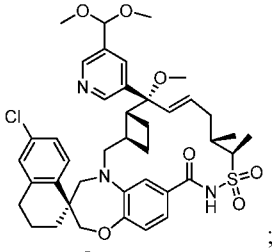
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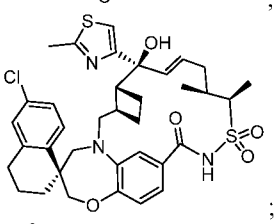
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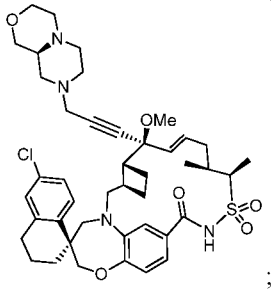
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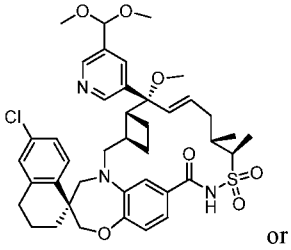
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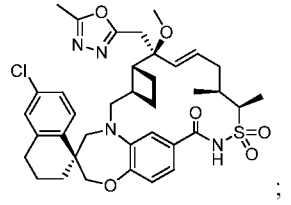
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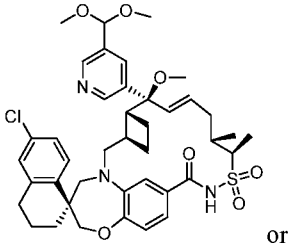
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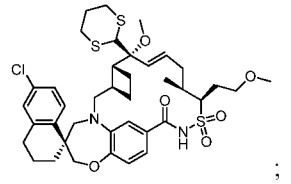
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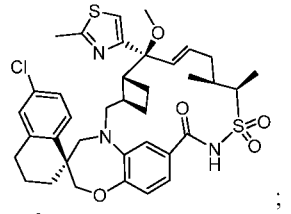
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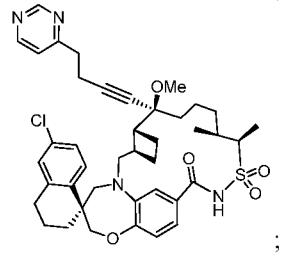
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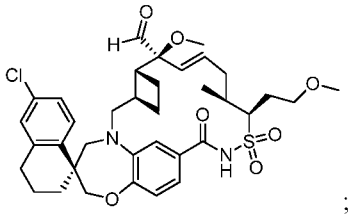
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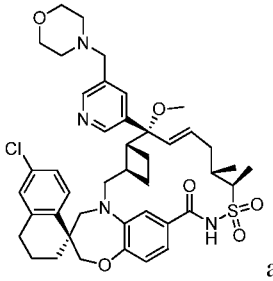
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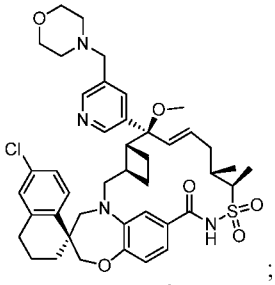
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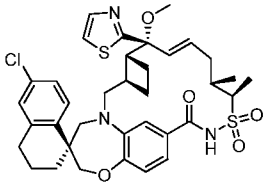
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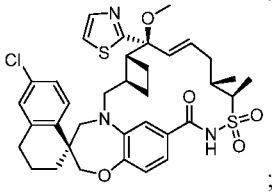
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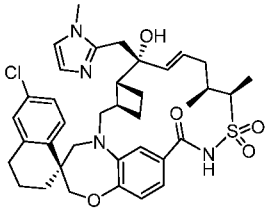
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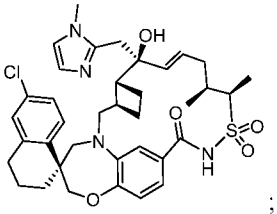
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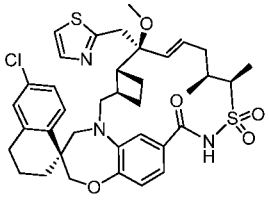
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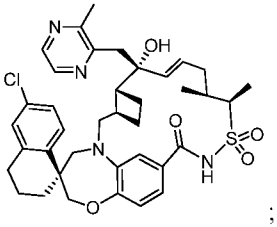
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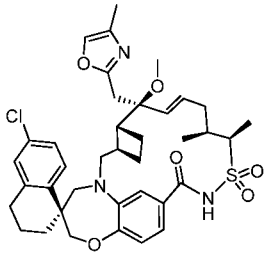
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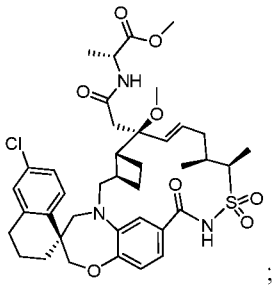
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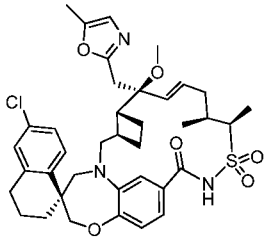
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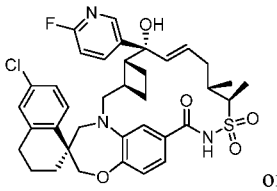
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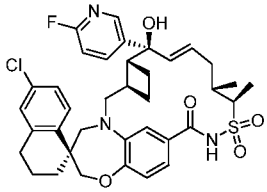
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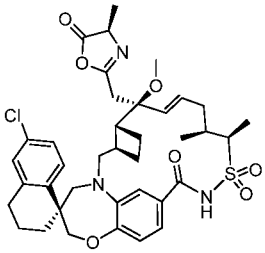
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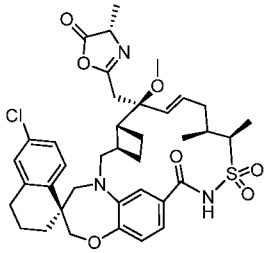
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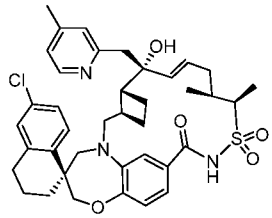
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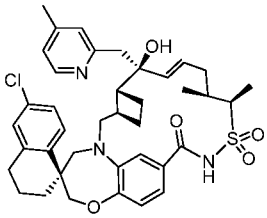
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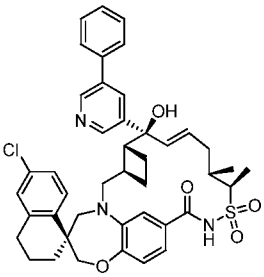
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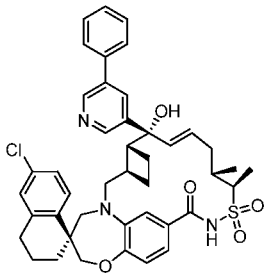
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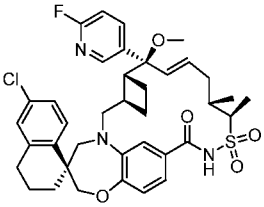
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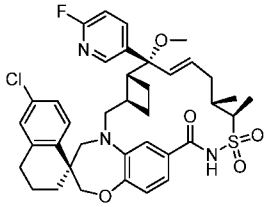
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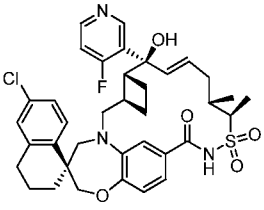
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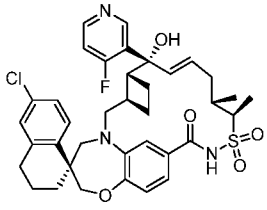
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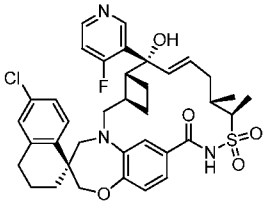
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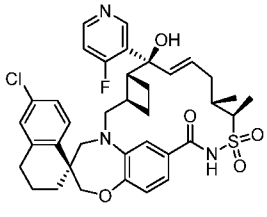
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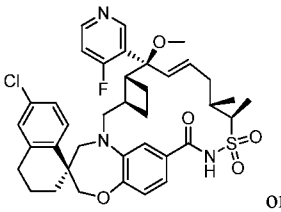
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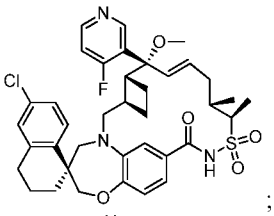
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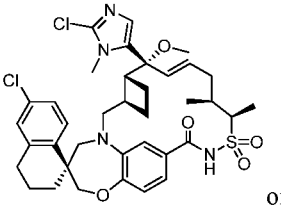
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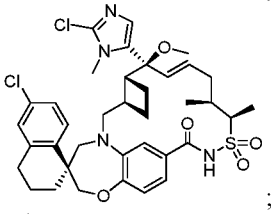
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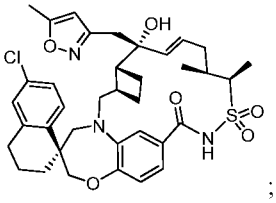
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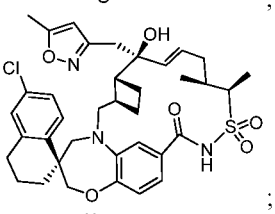
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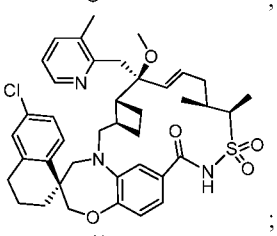
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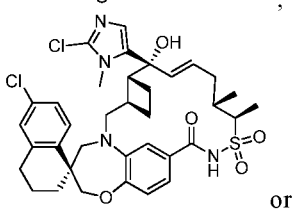
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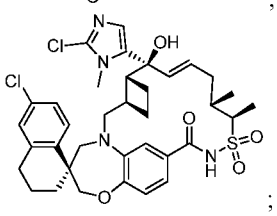
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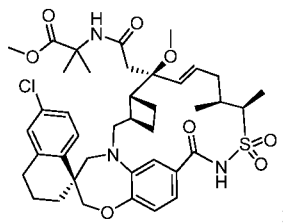
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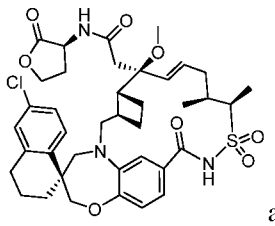
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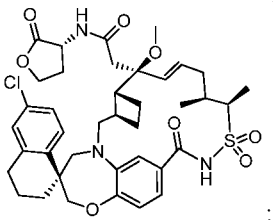
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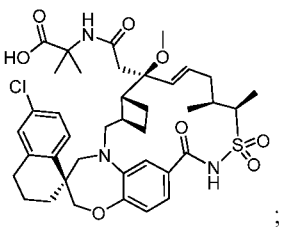
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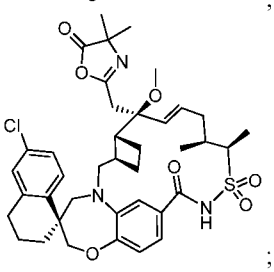
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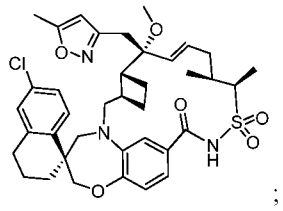
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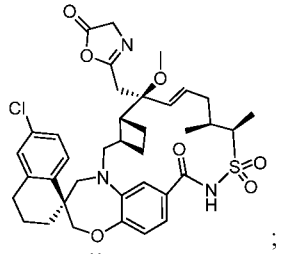
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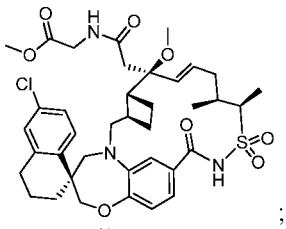
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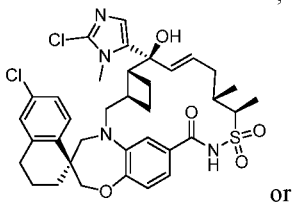
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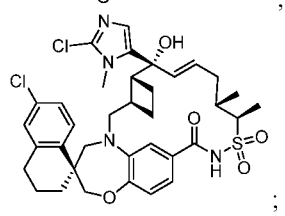
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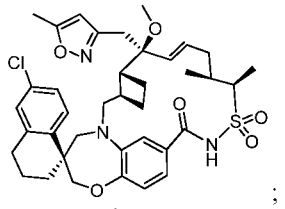
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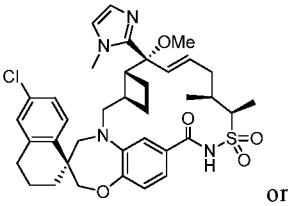
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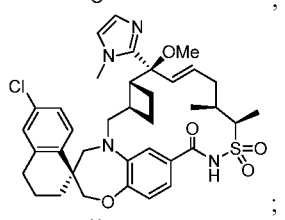
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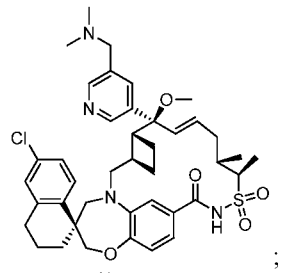
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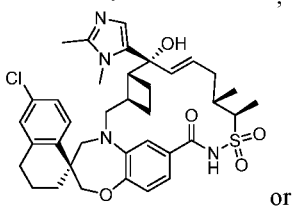
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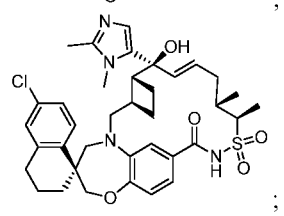
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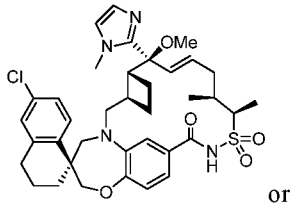
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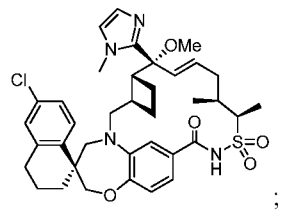
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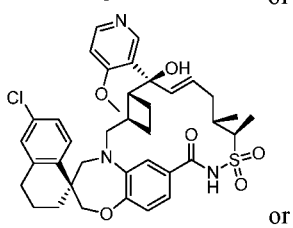
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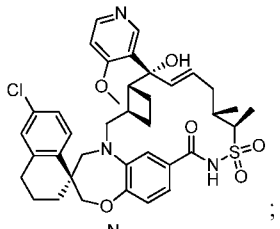
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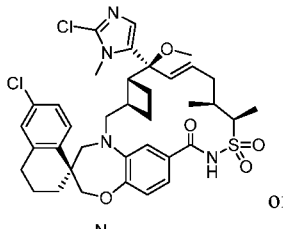
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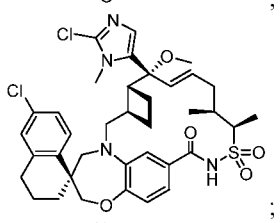
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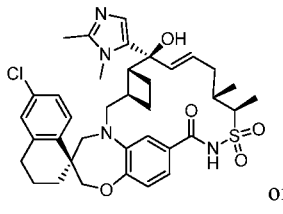
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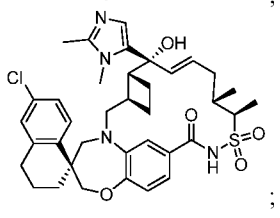
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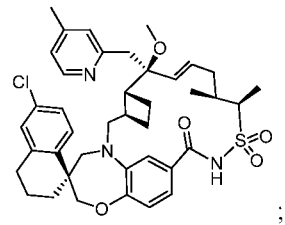
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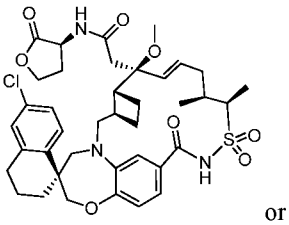
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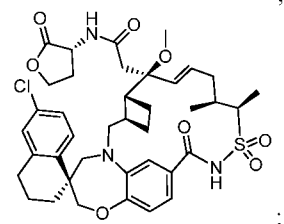
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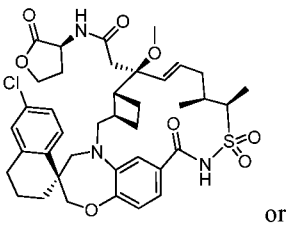
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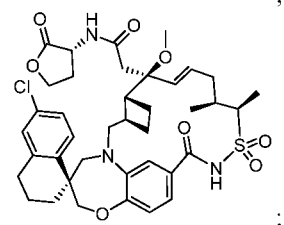
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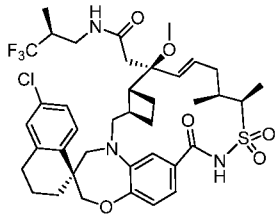
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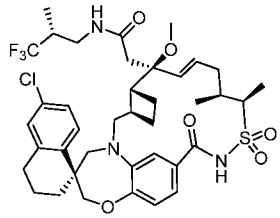
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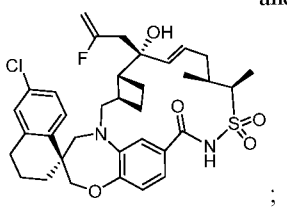
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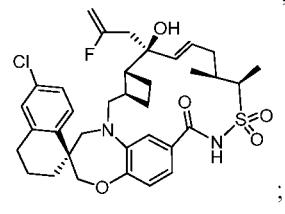
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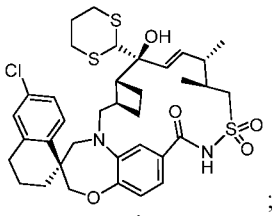
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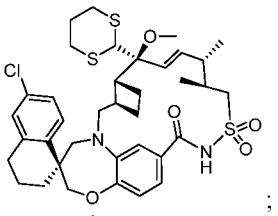
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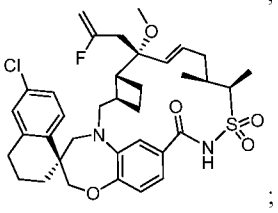
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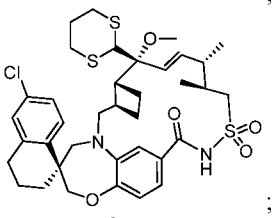
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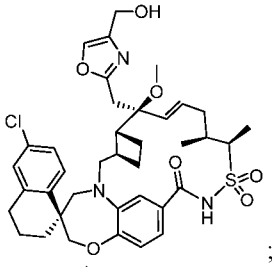
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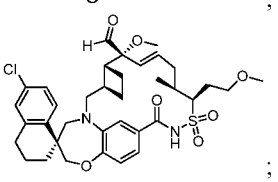
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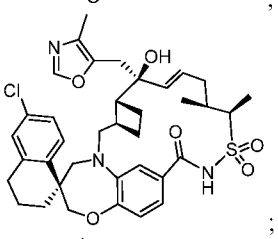
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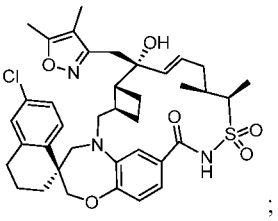
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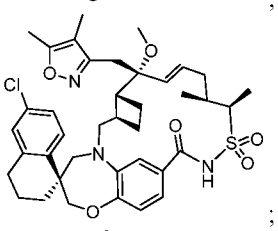
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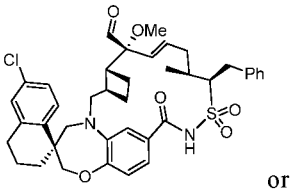
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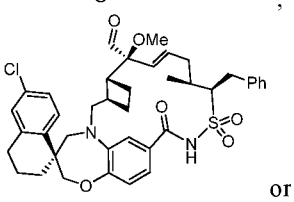
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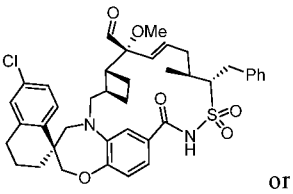
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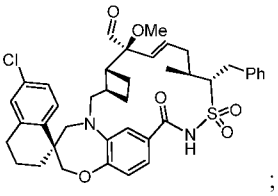
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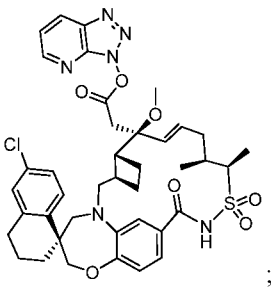
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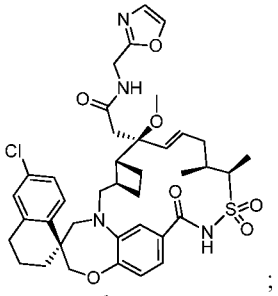
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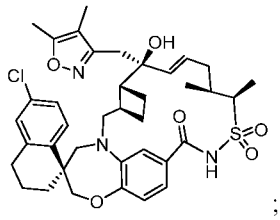
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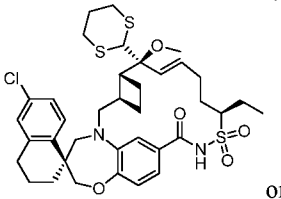
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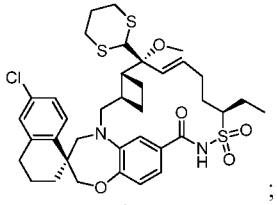
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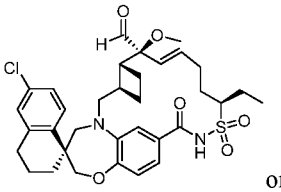
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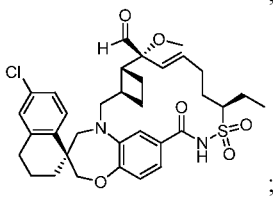
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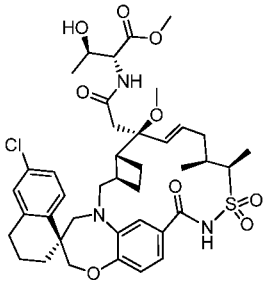
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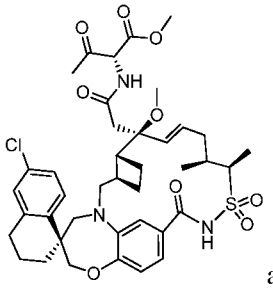
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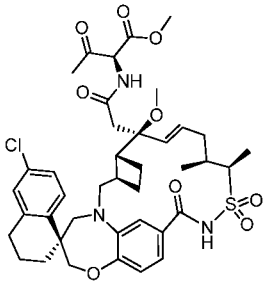
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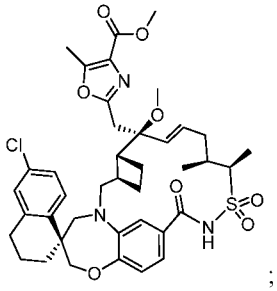
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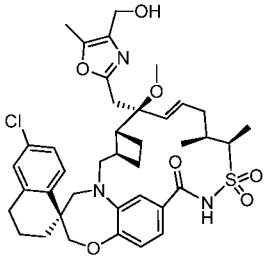
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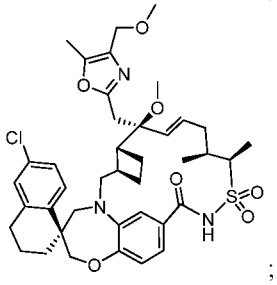
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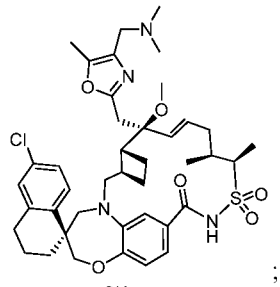
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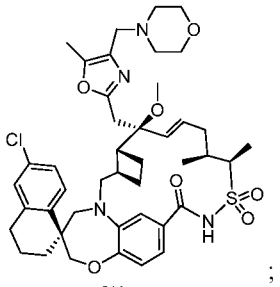
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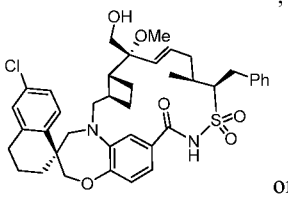
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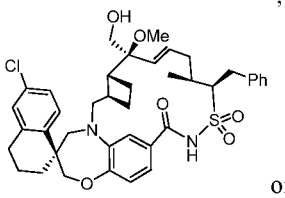
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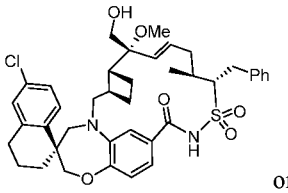
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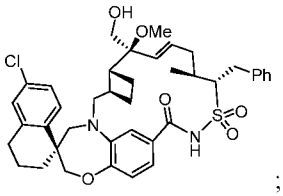
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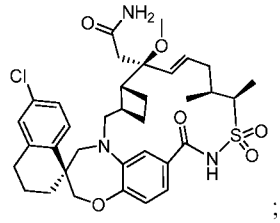
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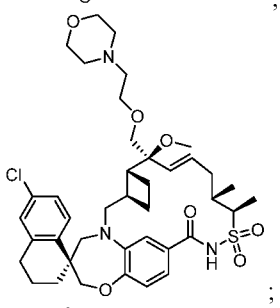
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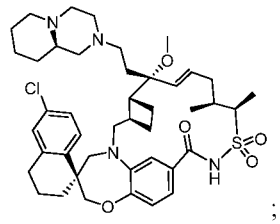
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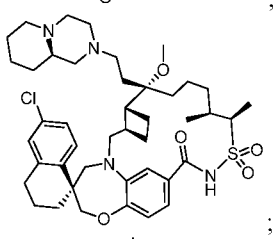
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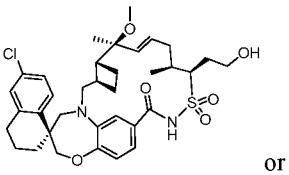
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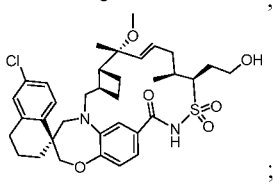
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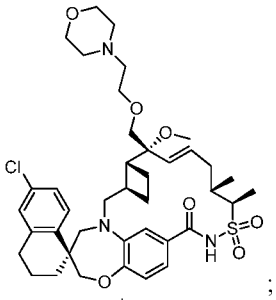
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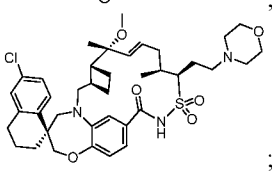
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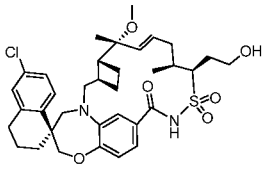
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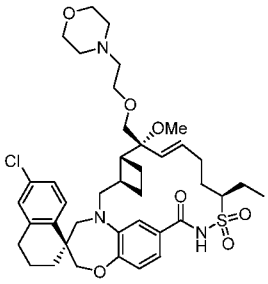
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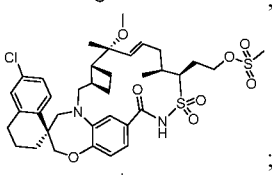
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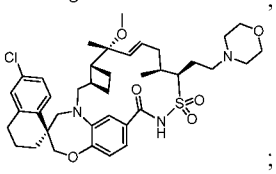
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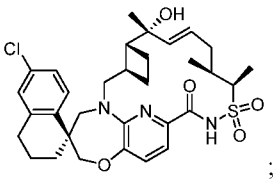
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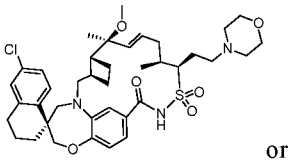
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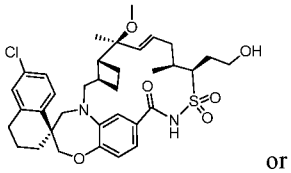
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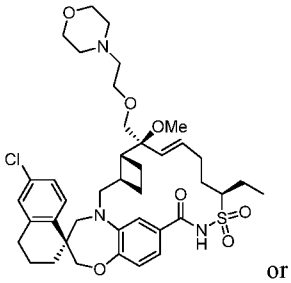
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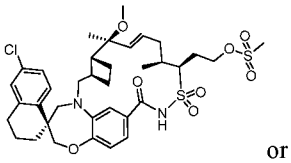
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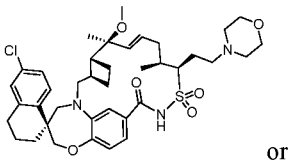
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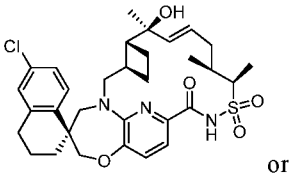
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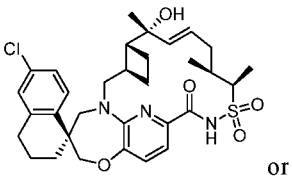
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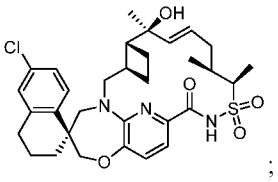
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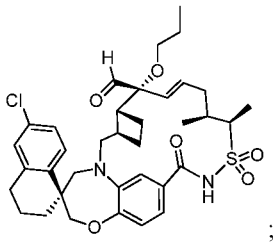
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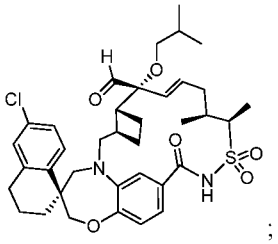
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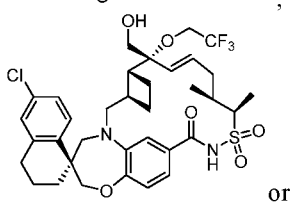
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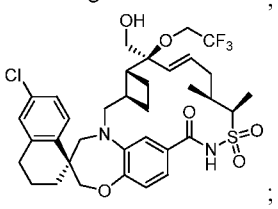
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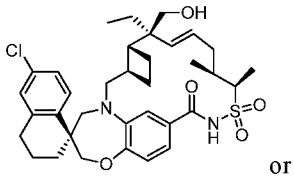
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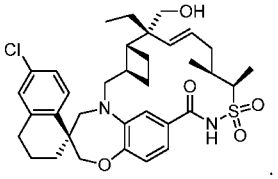
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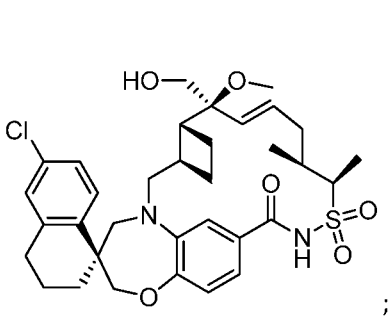
or a stereoisomer thereof; a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof.

91. Another embodiment of the present invention comprises a compound, wherein the compound has a structure selected from: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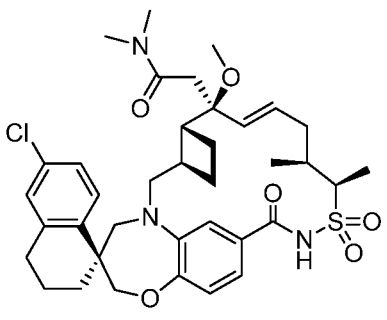
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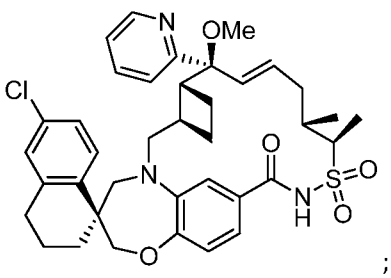
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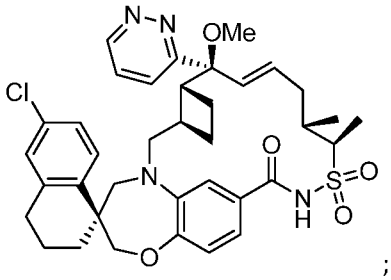
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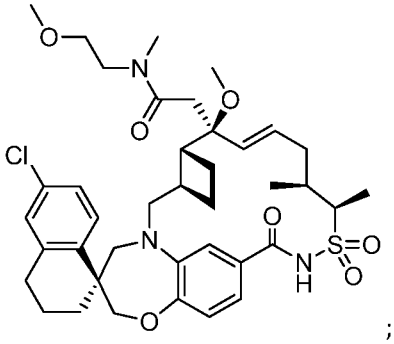
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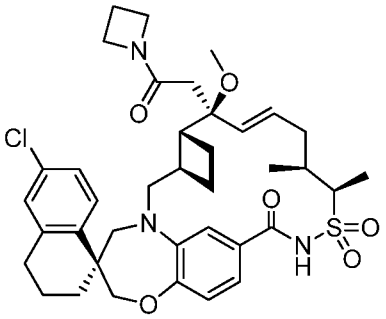
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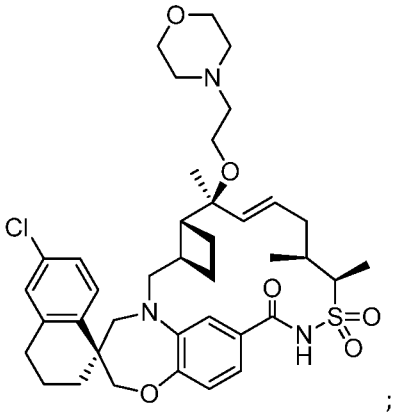
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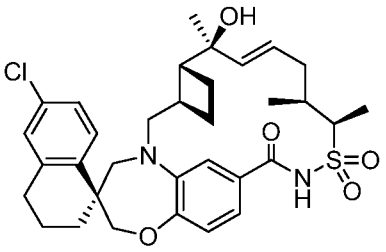
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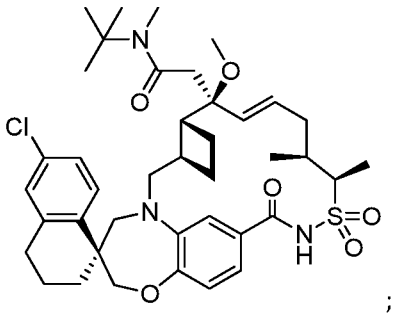
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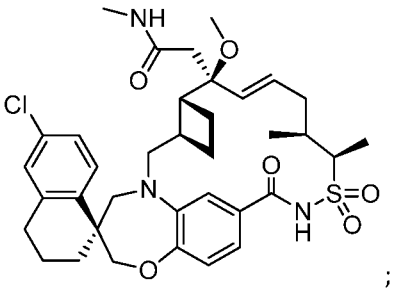
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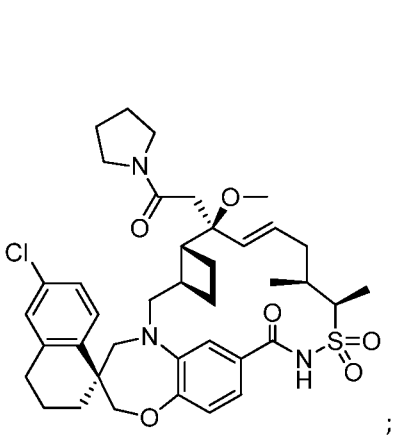
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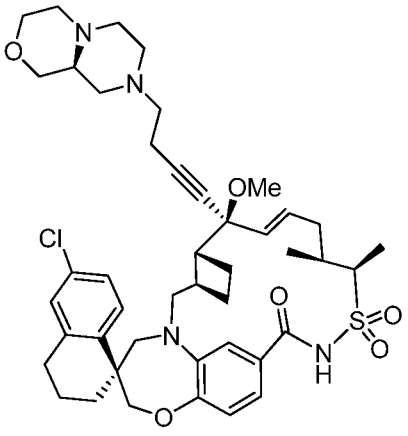
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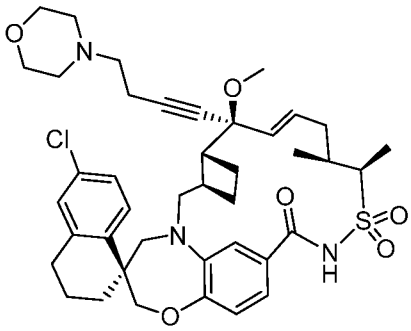
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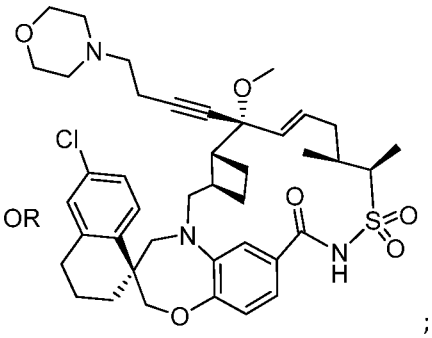
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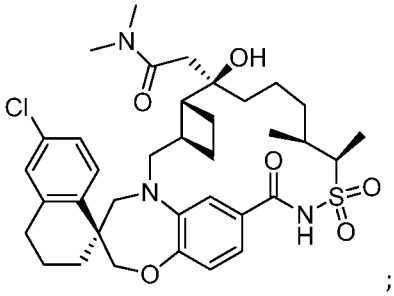
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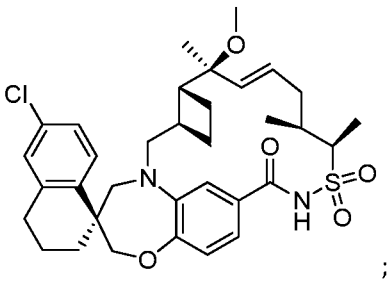
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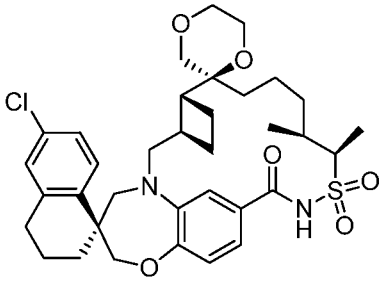
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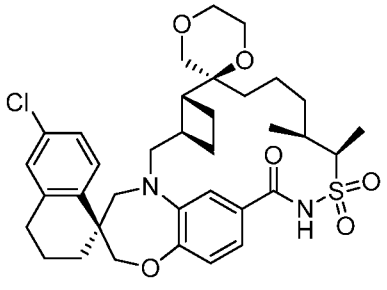
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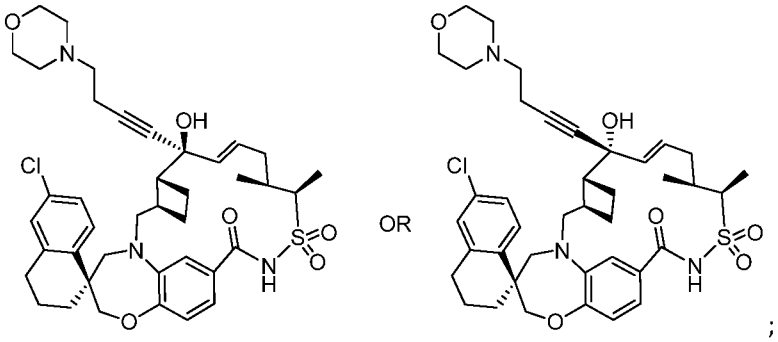

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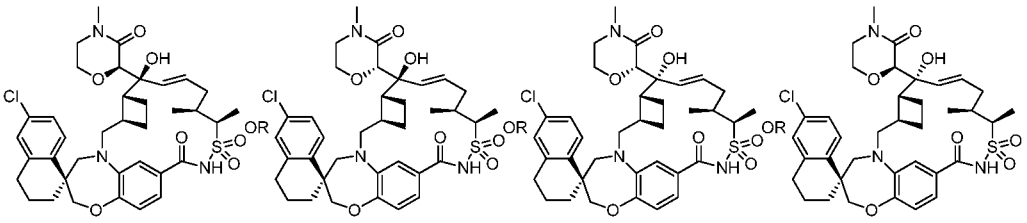

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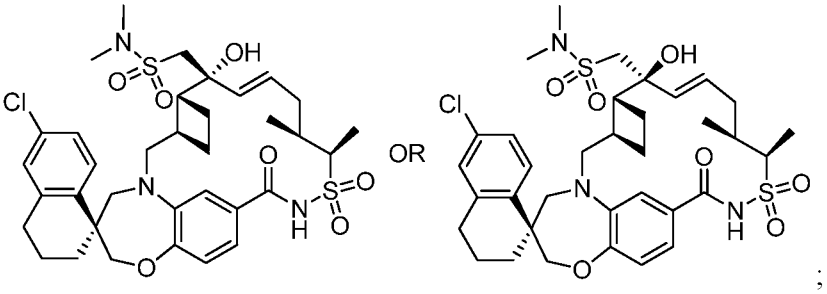


or ;

or a stereoisomer thereof; a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof.

92. The compound of embodiment 91 or the pharmaceutically acceptable salt thereof.

93. Another embodiment of the present invention comprises a pharmaceutical composition comprising the compound of any one of embodiments 1-92 or the pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

94. Another embodiment of the present invention comprises a method of treating cancer, the method comprising: administering to a patient in need thereof a therapeutically effective amount of the compound of any of embodiments 1-92 or a pharmaceutically acceptable salt thereof.

95. The method of embodiment 94, wherein the cancer is a hematologic malignancy.

96. The method of embodiment 94, wherein the cancer is selected from the group consisting of breast cancer, colorectal cancer, skin cancer, melanoma, ovarian cancer, kidney cancer, lung cancer, non-small cell lung cancer, lymphoma, non-Hodgkin's lymphoma, myeloma, multiple myeloma, leukemia, and acute myelogenous leukemia.

97. The method of embodiment 94, wherein the cancer is multiple myeloma.

98. The method of embodiment 94, further comprising administering to the patient in need thereof a therapeutically effective amount of an additional pharmaceutically active compound.

99. The method of embodiment 98, wherein the additional pharmaceutically active compound is carfilzomib.

100. The method of embodiment 98, wherein the additional pharmaceutically active compound is venetoclax.

101. The method of embodiment 98, wherein the additional pharmaceutically active compound is cytarabine.

102. Another embodiment of the present invention comprises a use of a compound according to any one of Embodiments 1-92 for treating cancer in a subject.

103. Another embodiment of the present invention comprises a compound according to any one of Embodiments 1-92 in the preparation of a medicament for treating cancer.

104. The compound according to Embodiment 103, wherein the cancer is a hematologic malignancy.

105. The compound according to embodiment 102, wherein the cancer is selected from the group consisting of breast cancer, colorectal cancer, skin cancer, melanoma, ovarian cancer, kidney cancer, lung cancer, non-small cell lung cancer, lymphoma, non-Hodgkin's lymphoma, myeloma, multiple myeloma, leukemia, and acute myelogenous leukemia.

106. The compound according to Embodiment 102, wherein the cancer is multiple myeloma.

107. The compound according to Embodiment 102, wherein the cancer is acute myelogenous leukemia.

108. The compound according to Embodiment 102, wherein the cancer is non-Hodgkin's lymphoma.

Another embodiment of the present invention is directed to a method of inhibiting myeloid cell leukemia 1 protein (Mcl-1) of a cell comprising contacting the cell with the compound of Formula I in an effective amount to inhibit the Mcl-1, in conjunction with any of the above or below embodiments.. In one embodiment, the contacting is *in vitro*. In another embodiment, the contacting is *in vivo*. In one embodiment, the contacting comprises administering the compound to a subject. In one embodiment, the administering is oral, parenteral, via injection, via inhalation, transdermal, or transmucosal. In one embodiment, the subject suffers from cancer.

One embodiment of the present invention is directed to a method of the treatment of cancer, comprising administering to a patient in need thereof a therapeutically effective amount of the compound of Formula I or a pharmaceutical composition comprising the compound of Formula I, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, in conjunction with any of the above or below embodiments. In one embodiment, the cancer is a hematologic malignancy. In one embodiment, the cancer is selected from the group consisting of breast cancer, colorectal cancer, skin cancer, melanoma, ovarian cancer, kidney cancer, lung cancer, non-small cell lung cancer, lymphoma, non-Hodgkin's lymphoma, myeloma, multiple myeloma, leukemia, and acute myelogenous leukemia. In one embodiment, the cancer is multiple myeloma. In another embodiment, the method further comprises the step of administering to the patient in need thereof a therapeutically effective amount of at least one additional pharmaceutically active compound. In one embodiment, the additional pharmaceutically active compound is carfilzomib, in conjunction with any of the above embodiments.

The methods provided herein include the manufacture and use of pharmaceutical compositions, which include one or more of the compounds provided herein. Also included are the pharmaceutical compositions themselves.

In some Claims, a compound provided herein may contain one or more acidic functional groups and, thus, is capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable bases. The term "pharmaceutically acceptable salts" in these instances refers to the relatively non-toxic inorganic and organic base addition salts of a compound provided herein. These salts can likewise be prepared *in situ* during the final isolation and purification of the compound, or by separately reacting the purified compound in its free acid form with a suitable base, such as the hydroxide, carbonate, or bicarbonate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary, or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts, and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, and the like (see, for example, Berge et al., supra).

Wetting agents, emulsifiers, and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring, and perfuming agents, preservatives and antioxida

Examples of pharmaceutically acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite, and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

A pharmaceutical composition may also contain adjuvants such as preservatives, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of

various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include tonicity-adjusting agents, such as sugars and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of one or more compounds provided herein, it is desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. For example, delayed absorption of a parenterally administered compound can be accomplished by dissolving or suspending the compound in an oil vehicle.

The compounds of the present invention are administered to a patient in a therapeutically effective amount. The compounds can be administered alone or as part of a pharmaceutically acceptable composition or formulation. In addition, the compounds or compositions can be administered all at once, as for example, by a bolus injection, multiple times, such as by a series of tablets, or delivered substantially uniformly over a period of time, as for example, using transdermal delivery. The dose of the compound or composition can be varied over time. All combinations, delivery methods and administration sequences are contemplated.

The compounds of the present invention and in some Claims, other additional pharmaceutically active compounds, can be administered to a patient either orally, rectally, parenterally, (for example, intravenously, intramuscularly, or subcutaneously) intracisternally, intravaginally, intraperitoneally, intravesically, locally (for example, powders, ointments or drops), or as a buccal or nasal spray. All methods that are used by those skilled in the art to administer a pharmaceutically active agent are contemplated.

Compositions prepared as described herein can be administered in various forms, depending on the disorder to be treated and the age, condition, and body weight of the patient, as is well known in the art. For example, where the compositions are to be administered orally, they may be formulated as tablets, capsules, granules, powders, or syrups; or for parenteral administration, they may

be formulated as injections (intravenous, intramuscular, or subcutaneous), drop infusion preparations, or suppositories. For application by the ophthalmic mucous membrane route, they may be formulated as eye drops or eye ointments. These formulations can be prepared by conventional means in conjunction with the methods described herein, and, if desired, the active ingredient may be mixed with any conventional additive or excipient, such as a binder, a disintegrating agent, a lubricant, a corrigent, a solubilizing agent, a suspension aid, an emulsifying agent, or a coating agent.

Formulations suitable for oral administration may be in the form of capsules (e.g., gelatin capsules), cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, troches, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert matrix, such as gelatin and glycerin, or sucrose and acacia) and/or as mouthwashes, and the like, each containing a predetermined amount of a compound provided herein as an active ingredient. A composition may also be administered as a bolus, electuary, or paste. Oral compositions generally include an inert diluent or an edible carrier.

Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of an oral composition. In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules, and the like), the active ingredient can be mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, cyclodextrins, lactose, sucrose, saccharin, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, microcrystalline cellulose, gum tragacanth, alginates, gelatin, polyvinyl pyrrolidone, sucrose, and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato, corn, or tapioca starch, alginic acid, Primogel, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such

as, for example, acetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such a talc, calcium stearate, magnesium stearate, Sterotes, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; (10) a glidant, such as colloidal silicon dioxide; (11) coloring agents; and (12) a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. In the case of capsules, tablets, and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols, and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of a powdered compound moistened with an inert liquid diluent.

Tablets, and other solid dosage forms, such as dragees, capsules, pills, and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes, microspheres, and/or nanoparticles. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric

substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups, and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents, and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols, and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming, and preservative agents.

Suspensions, in addition to the active compound(s) may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Pharmaceutical compositions suitable for parenteral administration can include one or more compounds provided herein in combination with one or more pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

In one Claim, the IV formulation consists of a composition containing hydroxypropyl beta cyclodextrin within a pH range between 8–10 as a buffered or unbuffered solution. The IV formulation can be formulated as a sterile solution ready for injection, a sterile solution ready for dilution into an IV admixture or a sterile solid for reconstituion. The API in the IV formulation may exist as a free acid/base or an in situ salt.

Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions provided herein include water for injection (e.g., sterile water for injection), bacteriostatic water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol such as liquid polyethylene glycol, and the like), sterile buffer (such as citrate buffer), and suitable mixtures thereof, vegetable oils, such as olive oil, injectable organic esters, such as ethyl oleate, and Cremophor EL™ (BASF, Parsippany, NJ). In all cases, the composition must be sterile and should be fluid to the extent that easy syringability exists. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

The composition should be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, and sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent that delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle, which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the methods of preparation are freeze-drying (lyophilization), which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Injectable depot forms can be made by forming microencapsule or nanoencapsule matrices of a compound provided herein in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes, microemulsions or nanoemulsions, which are compatible with body tissue.

For administration by inhalation, the compounds can be delivered in the form of an aerosol spray from a pressured container or dispenser that contains a suitable propellant (e.g., a gas such as carbon dioxide) or a nebulizer. Such methods include those described in U.S. Patent No. 6,468,798. Additionally, intranasal delivery can be accomplished, as described in, inter alia, Hamajima et al., *Clin. Immunol. Immunopathol.*, 88(2), 205-10 (1998). Liposomes (e.g., as described in U.S. Patent No. 6,472,375, which is incorporated herein by reference in its entirety), microencapsulation and nanoencapsulation can also be used. Biodegradable targetable microparticle delivery systems or biodegradable targetable nanoparticle delivery systems can also be used (e.g., as described in U.S. Patent No. 6,471,996, which is incorporated herein by reference in its entirety).

Systemic administration of a therapeutic compound as described herein can also be by transmucosal or transdermal means. Dosage forms for the topical or transdermal administration of a compound provided herein include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches, and inhalants. The active component may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants which may be required. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of

nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

The ointments, pastes, creams, and gels may contain, in addition to one or more compounds provided herein, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc, and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to a compound provided herein, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates, and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

A compound provided herein can be administered by aerosol. This is accomplished by preparing an aqueous aerosol, liposomal preparation, or solid particles containing a compound or composition provided herein. A nonaqueous (e.g., fluorocarbon propellant) suspension could be used. In some Claims, sonic nebulizers are used because they minimize exposing the agent to shear, which can result in degradation of the compound.

Ordinarily, an aqueous aerosol can be made by formulating an aqueous solution or suspension of the agent together with conventional pharmaceutically acceptable carriers and stabilizers. The carriers and stabilizers vary with the requirements of the particular composition, but typically include nonionic surfactants (TWEEN®(polysorbates), PLURONIC® (poloxamers), sorbitan esters, lecithin, CREMOPHOR®(polyethoxylates)), pharmaceutically acceptable co-solvents such as polyethylene glycol, innocuous proteins like serum albumin, sorbitan esters, oleic acid, lecithin, amino acids such as glycine, buffers, salts, sugars, or sugar alcohols. Aerosols generally are prepared from isotonic solutions.

Transdermal patches have the added advantage of providing controlled delivery of a compound provided herein to the body. Such dosage forms can be made by dissolving or dispersing the agent in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin.

The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

The pharmaceutical compositions can also be prepared in the form of suppositories or retention enemas for rectal and/or vaginal delivery. Formulations presented as a suppository can be prepared by mixing one or more compounds provided herein with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, glycerides, polyethylene glycol, a suppository wax or a salicylate, which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active agent. Formulations which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams, or spray formulations containing such carriers as are known in the art to be appropriate.

In one claim, the therapeutic compounds are prepared with carriers that will protect the therapeutic compounds against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Such formulations can be prepared using standard techniques, or obtained commercially (e.g., from Alza Corporation and Nova Pharmaceuticals, Inc). Liposomal suspensions (including liposomes targeted to selected cells with monoclonal antibodies to cellular antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811, which is incorporated herein by reference in its entirety for all purposes.

The compounds of the present invention are used in the treatment of diseases, disorders or symptoms mediated by Mcl-1 inhibition. Examples of diseases, disorders or symptoms mediated by Mcl-1 inhibition include, but are not limited to, cancers. Non-limiting examples of cancers include breast cancer, colorectal cancer, skin cancer, melanoma, ovarian cancer, kidney cancer, lung

cancer, non-small cell lung cancer, lymphoma, non-Hodgkin's lymphoma, myeloma, multiple myeloma, leukemia, and acute myelogenous leukemia.

The cancers can include carcinomas (originating in the outer layer of cells of the skin and internal membranes, e.g., breasts, kidneys, lungs, skin); sarcomas (arising from connective tissue such as bone, muscle, cartilage, and blood vessels), and hematologic malignancies (e.g., lymphomas and leukemias, which arise in the blood or blood-forming organs such as the spleen, lymph nodes, and bone marrow). Cancer cells can include, for example, tumor cells, neoplastic cells, malignant cells, metastatic cells, and hyperplastic cells.

In an Claim, the disease, disorder or symptom is a hyperproliferative disorder, e.g., a lymphoma, leukemia, carcinoma (e.g., renal, breast, lung, skin), multiple myeloma, or a sarcoma. In one Claim, the leukemia is acute myeloid leukemia. In one Claim, the hyperproliferative disorder is a relapsed or refractory cancer.

Actual dosage levels of the active ingredients in the pharmaceutical compositions provided herein may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

The specific dosage and dosage range depends on a number of factors, including the requirements of the patient, the severity of the condition or disease being treated, the pharmacokinetic characteristics of the compound(s) employed, and the route of administration. In some Claims, the compositions provided herein can be provided in an aqueous solution containing about 0.1-10% w/v of a compound disclosed herein, among other substances, for parenteral administration. Typical dose ranges can include from about 0.01 to about 50 mg/kg of body weight per day, given in 1-4 divided doses. Each divided dose may contain the same or different compounds. The dosage will be a therapeutically effective amount depending on several factors including the overall health of a patient, and the formulation and route of administration of the selected compound(s).

Dosage forms or compositions containing a compound as described herein in the range of 0.005% to 100% with the balance made up from non-toxic carrier may be prepared. Methods for preparation of these compositions are known to those skilled in the art. The contemplated compositions may contain about 0.001%-100% active ingredient, in one Claim from about 0.1 to about 95%, in another Claim from about 75 to about 85%. Although the dosage will vary depending on the symptoms, age and body weight of the patient, the nature and severity of the disorder to be treated or prevented, the route of administration and the form of the drug, in general, a daily dosage of from about 0.01 to about 3,000 mg of the compound is recommended for an adult human patient, and this may be administered in a single dose or in divided doses. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect.

The pharmaceutical composition may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the disease being treated and may be determined empirically using known testing protocols or by extrapolation from in vivo or in vitro test data. It is to be noted that concentrations and dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular patient, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the Claimed compositions.

The precise time of administration and/or amount of the composition that will yield the most effective results in terms of efficacy of treatment in a given patient will depend upon the activity, pharmacokinetics, and bioavailability of a particular compound, physiological condition of the patient (including age, sex, disease type and stage, general physical condition, responsiveness to a given

dosage, and type of medication), route of administration, etc. However, the above guidelines can be used as the basis for fine-tuning the treatment, e.g., determining the optimum time and/or amount of administration, which will require no more than routine experimentation consisting of monitoring the patient and adjusting the dosage and/or timing

The compounds of the present invention can be administered alone, in combination with other compounds of the present invention, or with other pharmaceutically active compounds or agents. The other pharmaceutically active compounds/agents can be intended to treat the same disease or condition as the compounds of the present invention or a different disease or condition. If the patient is to receive or is receiving multiple pharmaceutically active compounds or agents, the compounds can be administered simultaneously, or sequentially.

The compounds of the present invention, or pharmaceutically acceptable salts thereof, may be used in combination with one or more additional pharmaceutically active compounds/agents.

One or more additional pharmaceutically active compounds or agents may be administered separately, as part of a multiple dose regimen, from the compound of Formula I (e.g., sequentially, e.g., on different overlapping schedules with the administration of one or more compounds of Formula I (including any subgenera or specific compounds thereof). In other Claims, the one or more additional compounds/agents may be part of a single dosage form, mixed together with the compound of Formula I in a single composition. In still another Claim, the one or more additional compounds/agents can be given as a separate dose that is administered at about the same time that one or more compounds of Formula I are administered (e.g., simultaneously with the administration of one or more compounds of Formula I (including any subgenera or specific compounds thereof). Both the compound of Formula I and the one or more additional compounds/agents can be present at dosage levels of between about 1 to 100%, and more preferably between about 5 to 95% of the dosage normally administered in a monotherapy regimen.

In a particular claim, the additional pharmaceutically active compound/agent is a compound or agent that can be used to treat a cancer. For example, the additional pharmaceutically active compound/agent can be selected from antineoplastic agents, anti-angiogenic agents, chemotherapeutic agents, and peptidal cancer therapy agents. In another Claim, the antineoplastic agents are selected from antibiotic-type agents, alkylating agents, antimetabolite agents, hormonal agents, immunological agents, interferon-type agents, kinase inhibitors, proteasome inhibitors, and combinations thereof. It is noted that the additional pharmaceutically active compound/agent may be a traditional small organic chemical molecule or can be a macromolecule such as a protein, antibody, peptibody, DNA, RNA or a fragment of such macromolecules.

Examples of additional pharmaceutically active compounds/agents that can be used in the treatment of cancers and that can be used in combination with one or more compounds of the present invention include: acemannan; aclarubicin; aldesleukin; alitretinoin; amifostine; amrubicin; amsacrine; anagrelide; arglabin; arsenic trioxide; BAM 002 (Novelos); bicalutamide; broxuridine; celmoleukin; cetrorelix; cladribine; clotrimazole; cytarabine; DA 3030 (Dong-A); daclizumab; denileukin diftitox; deslorelin; dilazep; docosanol; doxercalciferol; doxifluridine; bromocriptine; cytarabine; HIT diclofenac; interferon alfa; tretinoin; edelfosine; edrecolomab; eflornithine; emitefur; epirubicin; epoetin beta; etoposide phosphate; exisulind; fadrozole; finasteride; fludarabine phosphate; formestane; fotemustine; gallium nitrate; gemtuzumab zogamicin; gimeracil/oteracil/tegafur combination; glycopine; goserelin; heptaplatin; human chorionic gonadotropin; human fetal alpha fetoprotein; ibandronic acid; interferon alfa; interferon alfa natural; interferon alfa-2; interferon alfa-2a; interferon alfa-2b; interferon alfa-N1; interferon alfa-n3; interferon alfacon-1; interferon alpha natural; interferon beta; interferon beta-1a; interferon beta-1b; interferon gamma natural; interferon gamma-1a; interferon gamma-1b; interleukin-1 beta; iobenguane; irsogladine; lanreotide; LC 9018 (Yakult); leflunomide; lenograstim; lentinan sulfate; letrozole; leukocyte alpha interferon; leuprorelin; levamisole+fluorouracil; liarozole; lobaplatin; lonidamine; lovastatin; masoprocol; melarsoprol;

metoclopramide; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitoxantrone; molgramostim; nafarelin; naloxone+pentazocine; nartograstim; nedaplatin; nilutamide; noscapine; novel erythropoiesis stimulating protein; NSC 631570 octreotide; oprelvekin; osaterone; paclitaxel; pamidronic acid; peginterferon alfa-2b; 243rimethyl polysulfate sodium; pentostatin; picibanil; pirarubicin; rabbit antithymocyte polyclonal antibody; polyethylene glycol interferon alfa-2a; porfimer sodium; raltitrexed; rasburicase; rhenium Re 186 etidronate; RII retinamide; romurtide; samarium (153 Sm) lexidronam; sargramostim; sizofuran; sobuzoxane; sonermin; strontium-89 chloride; suramin; tasonermin; tazarotene; tegafur; temoporfin; teniposide; tetrachlorodecaoxide; thymalfasin; thyrotropin alfa; toremifene; tositumomab-iodine 131; treosulfan; tretinoin; trilostane; trimetrexate; triptorelin; trametinib; tumor necrosis factor alpha natural; ubenimex; bladder cancer vaccine; Maruyama vaccine; melanoma lysate vaccine; valrubicin; venetoclax; verteporfin; virulizin; zinostatin stimalamer; abarelix; AE 941 (Aeterna); ambamustine; antisense oligonucleotide; bcl-2 (Genta); APC 8015 (Dendreon); dexaminoglutethimide; diaziquone; EL 532 (Elan); EM 800 (Endorecherche); eniluracil; etanidazole; fenretinide; galocitabine; gastrin 17 immunogen; HLA-B7 gene therapy (Vical); granulocyte macrophage colony stimulating factor; histamine dihydrochloride; ibritumomab tiuxetan; ilomastat; IM 862 (Cytran); interleukin-2; iproxifene; LDI 200 (Milkhaus); leridistim; lintuzumab; CA 125 monoclonal antibody (Mab) (Biomira); cancer Mab (Japan Pharmaceutical Development); HER-2 and Fc Mab (Medarex); idiotypic 105AD7 Mab (CRC Technology); idiotypic CEA Mab (Trilex); LYM-1-iodine 131 Mab (Techniclone); polymorphic epithelial mucin-yttrium 90 Mab (Antisoma); marimastat; menogaril; mitumomab; motexafin gadolinium; MX 6 (Galderma); nolatrexed; P 30 protein; pegvisomant; porfiromycin; prinomastat; RL 0903 (Shire); rubitecan; satraplatin; sodium phenylacetate; sparfosic acid; SRL 172 (SR Pharma); SU 5416 (SUGEN); TA 077 (Tanabe); tetrathiomolybdate; thaliblastine; thrombopoietin; tin ethyl etiopurpurin; tirapazamine; cancer vaccine (Biomira); melanoma vaccine; melanoma oncolysate vaccine; viral melanoma cell lysates vaccine; valspodarl; fluorouracil; 5-

fluorouracil; 244rimethyla; imatinib; altretamine; cladibrine; cyclophosphamine; decarazine; irinotecan; mitosmycin; mitoxane; topotecan; vinorelbine; 244rimethyla; mithram; imiquimod; alemtuzmab; exemestane; bevacizumab; cetuximab; azacitidine; clofarabine; decitabine; desatinib; dexrazoxane; docetaxel; epirubicin; oxaliplatin; erlotinib; raloxifene; fulvestrant; letrozole; gefitinib; gemtuzumab; trastuzumab; gefitinib; ixabepilone; lapatinib; lenalidomide; aminolevulinic acid; temozolomide; nelarabine; sorafenib; nilotinib; pegaspargase; pemetrexed; rituximab; dasatinib; thalidomide; bexarotene; temsirolimus; bortezomib; 244rimethylam; oprozomib; vorinostat; capecitabine; zoledronic acid; anastrozole; sunitinib; aprepitant and nelarabine, or a pharmaceutically acceptable salt thereof.

Additional pharmaceutically active compounds/agents that can be used in the treatment of cancers and that can be used in combination with one or more compound of the present invention include: epoetin alfa; darbepoetin alfa; panitumumab; pegfilgrastim; palifermin; filgrastim; denosumab; ancestim; AMG 102; AMG 386; AMG 479; AMG 655; AMG 745; AMG 951; and AMG 706, or a pharmaceutically acceptable salt thereof.

In certain claims, a composition provided herein is conjointly administered with a chemotherapeutic agent . Suitable chemotherapeutic agents may include, natural products such as vinca alkaloids (e.g., vinblastine, vincristine, and vinorelbine), paclitaxel, epidipodophyllotoxins (e.g., etoposide and teniposide), antibiotics (e.g., dactinomycin (actinomycin D), daunorubicin, doxorubicin, and idarubicin), anthracyclines, mitoxantrone, bleomycins, plicamycin (mithramycin), mitomycin, enzymes (e.g., L-asparaginase which systemically metabolizes L-asparagine and deprives cells which do not have the capacity to synthesize their own asparagine), antiplatelet agents, antiproliferative/antimitotic alkylating agents such as nitrogen mustards (e.g., mechlorethamine, cyclophosphamide and analogs, melphalan, and chlorambucil), ethylenimines and methylmelamines (e.g., hexaamethylmelaamine and thiotepa), CDK inhibitors (e.g., seliciclib, UCN-01, P1446A-05, PD-0332991, dinaciclib, P27-00, AT-7519, RGB286638, and SCH727965), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine

(BCNU) and analogs, and streptozocin), trazenes-dacarbazinine (DTIC), antiproliferative/antimitotic antimetabolites such as folic acid analogs (e.g., methotrexate), pyrimidine analogs (e.g., fluorouracil, floxuridine, and cytarabine), purine analogs and related inhibitors (e.g., mercaptopurine, thioguanine, pentostatin and 2-chlorodeoxyadenosine), aromatase inhibitors (e.g., anastrozole, exemestane, and letrozole), and platinum coordination complexes (e.g., cisplatin and carboplatin), procarbazine, hydroxyurea, mitotane, aminoglutethimide, histone deacetylase (HDAC) inhibitors (e.g., trichostatin, sodium butyrate, apicidan, suberoyl anilide hydroamic acid, vorinostat, LBH 589, romidepsin, ACY-1215, and panobinostat), mTor inhibitors (e.g., temsirolimus, everolimus, ridaforolimus, and sirolimus), KSP(Eg5) inhibitors (e.g., Array 520), DNA binding agents (e.g., Zalypsis), PI3K delta inhibitor (e.g., GS-1101 and TGR-1202), PI3K delta and gamma inhibitor (e.g., CAL-130), multi-kinase inhibitor (e.g., TG02 and sorafenib), hormones (e.g., estrogen) and hormone agonists such as leutinizing hormone releasing hormone (LHRH) agonists (e.g., goserelin, leuprolide and triptorelin), BAFF-neutralizing antibody (e.g., LY2127399), IKK inhibitors, p38MAPK inhibitors, anti-IL-6 (e.g., CNTO328), telomerase inhibitors (e.g., GRN 163L), aurora kinase inhibitors (e.g., MLN8237), cell surface monoclonal antibodies (e.g., anti-CD38 (HUMAX-CD38), anti-CS1 (e.g., elotuzumab), inhibitors of KRAS including covalent inhibiors of KRAS G12C, MEK inhibitor, including trametinib, HSP90 inhibitors (e.g., 17 AAG and KOS 953), P13K / Akt inhibitors (e.g., perifosine), Akt inhibitor (e.g., GSK-2141795), PKC inhibitors (e.g., enzastaurin), FTIs (e.g., Zarnestra™), anti-CD138 (e.g., BT062), Torc1/2 specific kinase inhibitor (e.g., INK128), kinase inhibitor (e.g., GS-1101), ER/UPR targeting agent (e.g., MKC-3946), cFMS inhibitor (e.g., ARRY-382), JAK1/2 inhibitor (e.g., CYT387), PARP inhibitor (e.g., olaparib and veliparib (ABT-888)), BCL-2 antagonist. Other chemotherapeutic agents may include mechlorethamine, camptothecin, ifosfamide, tamoxifen, raloxifene, gemcitabine, navelbine, sorafenib, or any analog or derivative variant of the foregoing.

The compounds of the present invention may also be used in combination with radiation therapy, hormone therapy, surgery and immunotherapy, which therapies are well known to those skilled in the art.

In certain claims, a pharmaceutical composition provided herein is conjointly administered with a steroid. Suitable steroids may include, but are not limited to, 21-acetoxypregnenolone, alclometasone, algestone, amcinonide, beclomethasone, betamethasone, budesonide, chloroprednisone, clobetasol, clocortolone, cloprednol, corticosterone, cortisone, cortivazol, deflazacort, desonide, desoximetasone, dexamethasone, diflorasone, diflucortolone, difuprednate, enoxolone, fluazacort, flucloronide, flumethasone, flunisolide, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluocortolone, fluorometholone, fluperolone acetate, fluprednidene acetate, fluprednisolone, flurandrenolide, fluticasone propionate, formocortal, halcinonide, halobetasol propionate, halometasone, hydrocortisone, loteprednol etabonate, mazipredone, medrysone, meprednisone, methylprednisolone, mometasone furoate, paramethasone, prednicarbate, prednisolone, prednisolone 25-diethylaminoacetate, prednisolone sodium phosphate, prednisone, prednival, prednylidene, rimexolone, tixocortol, triamcinolone, triamcinolone acetonide, triamcinolone benetonide, triamcinolone hexacetonide, and salts and/or derivatives thereof.In a particular Claim, the compounds of the present invention can also be used in combination with additional pharmaceutically active agents that treat nausea. Examples of agents that can be used to treat nausea include: dronabinol; granisetron; metoclopramide; ondansetron; and prochlorperazine; or a pharmaceutically acceptable salt thereof.

As one aspect of the present invention contemplates the treatment of the disease/conditions with a combination of pharmaceutically active compounds that may be administered separately, the invention further relates to combining separate pharmaceutical compositions in kit form. The kit comprises two separate pharmaceutical compositions: a compound of the present invention, and a second pharmaceutical compound. The kit comprises a container for containing the separate compositions such as a divided bottle or a divided foil packet. Additional

examples of containers include syringes, boxes, and bags. In some Claims, the kit comprises directions for the use of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing health care professional.

The compounds of the present invention can be administered as pharmaceutically acceptable salts, esters, amides or prodrugs. The term "salts" refers to inorganic and organic salts of compounds of the present invention. The salts can be prepared in situ during the final isolation and purification of a compound, or by separately reacting a purified compound in its free base or acid form with a suitable organic or inorganic base or acid and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, palmitiate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts, and the like. The salts may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, and the like, as well as non-toxic ammonium, quaternary ammonium, and amine cations including, but not limited to, ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, 247rimethylamine, ethylamine, and the like. See, for example, S. M. Berge, et al., "Pharmaceutical Salts," J Pharm Sci, 66: 1-19 (1977).

The term "prodrug" means compounds that are transformed in vivo to yield a compound of the present invention. The transformation may occur by various mechanisms, such as through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

To illustrate, if the compound of the invention contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as (C_1-C_8 alkyl, (C_2-C_{12})alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)aminomethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C_1-C_2)alkylamino(C_2-C_3)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C_1-C_2)alkyl, N,N-di(C_1-C_2)alkylcarbamoyl-(C_1-C_2)alkyl and piperidino-, pyrrolidino- or morpholino(C_2-$_3$)alkyl.

Similarly, if a compound of the present invention comprises an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as (C_1-C_6)alkanoyloxymethyl, 1-((C_1-C_6)alkanoyloxy)ethyl, 1-methyl-1-((C_1-C_6)alkanoyloxy)ethyl, (C_1-C_6)alkoxycarbonyloxymethyl, N-(C_1-C_6)alkoxycarbonylaminomethyl, succinoyl, (C_1-C_6)alkanoyl, α-amino(C_1-C_4)alkanoyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, –P(O)(OH)$_2$, –P(O)(O(C_1-C_6)alkyl)$_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

The compounds of the present invention may contain asymmetric or chiral centers, and therefore, exist in different stereoisomeric forms. It is contemplated that all stereoisomeric forms of the compounds as well as mixtures thereof, including racemic mixtures, form part of the present invention. In addition, the present invention contemplates all geometric and positional isomers. For example, if the compound contains a double bond, both the cis and trans forms (designated as Z and E, respectively), as well as mixtures, are contemplated.

Mixture of stereoisomers, such as diastereomeric mixtures, can be separated into their individual stereochemical components on the basis of their physical chemical differences by known methods such as chromatography and/or fractional crystallization. Enantiomers can also be separated by converting the enantiomeric mixture into a diasteromeric mixture by reaction with an appropriate optically active compound (e.g., an alcohol), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers.

The compounds of the present invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water (hydrate), ethanol, and the like. The present invention contemplates and encompasses both the solvated and unsolvated forms.

It is also possible that compounds of the present invention may exist in different tautomeric forms. All tautomers of compounds of the present invention are contemplated. Those skilled in the art will recognize that the compound names and structures contained herein may be based on a particular tautomer of a compound. While the name or structure for only a particular tautomer may be used, it is intended that all tautomers are encompassed by the present invention, unless stated otherwise.

It is also intended that the present invention encompass compounds that are synthesized in vitro using laboratory techniques, such as those well known to synthetic chemists; or synthesized using in vivo techniques, such as through metabolism, fermentation, digestion, and the like. It is also contemplated that the compounds of the present invention may be synthesized using a combination of in vitro and in vivo techniques.

The compounds of the present invention may exist in various solid states including crystalline states and as an amorphous state. The different crystalline states, also called polymorphs, and the amorphous states of the present compounds are contemplated as part of this invention.

EXAMPLES

The examples presented below illustrate specific Claims of the present invention. These examples are meant to be representative and are not intended to limit the scope of the Claims in any manner.

The following abbreviations may be used herein:

~	about
Ac	acetate
Ac_2O	acetic anhydride
AcOH	acetic acid
Al_2O_3	aluminum oxide
br	broad
Boc	tert-butyloxycarbonyl
$B(OiPr)_3$	triisopropyl borate
$B(Oallyl)_3$	triallyl borate
$B(OCH_2CF_3)_3$	tris(2,2,2-trifluoroethyl) borate
$B(On\text{-}Bu)_3$	tri-*n*-butyl borate
Calcd	calculated
CO_2	carbon dioxide
CSA	10-camphorsulfonic acid
d	day or doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DCM	dichloromethane
DEA	diethylamine
Dess-Martin periodinane	1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3-(1H)-one
DIPEA or DIEA	diisopropylethylamine
DMA	N,N-dimethylacetamide
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide

EDC	N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide
ee or e.e.	enantiomeric excess
ELISA	enzyme-linked immunosorbent assay
eq or equiv	equivalent
ESI or ES	electrospray ionization
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
Et_3N	triethylamine
EtOH	ethyl alcohol
EtI	ethyl iodide
g	gram(s)
GC	gas chromatography
h	hour(s)
H_2	hydrogen gas
HCl	hydrochloric acid
^1H NMR	proton nuclear magnetic resonance spectroscopy
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
H_2O	water
HPLC	high performance liquid chromatography
H_2SO_4	sulfuric acid
Hz	Hertz
IP	intraperitoneal
IPA	isopropyl alcohol
K_2CO_3	potassium carbonate
KF	Karl Fischer titration
KHMDS	potassium hexamethyldisilazide

KOAc	potassium acetate
KOH	potassium hydroxide
K_3PO_4	potassium phosphate
KOtBu	potassium tert-butoxide
L	liter
LAH	lithium aluminium hydride
LCMS, LC-MS, or LC/MS	liquid chromatography mass spectrometry
LHMDS	lithium hexamethyldisilazide
m	multiplet
mm	millimeter
M	molar (mol/L) or mass
Me	methyl
MeCN	acetonitrile
MeI	iodomethane
MeOH	methyl alcohol
MeTHF	2-methyltetrahydrofuran
Me_3SI	trimethylsulfonium iodide
$MeNH_2$	methylamine
Me_2NH	dimethylamine
mg	milligram(s)
$MgSO_4$	magnesium sulphate
MHz	megahertz
µm	micrometer
µL	microliter
min	minute(s)
mL	milliliter(s)
mm	millimeter(s)
mol	mole
MS	mass spectrometry
MSA	methanesulfonic acid
MsCl	methanesulfonyl chloride

MTBE	methyl tert-butyl ether
m/z	mass-to-charge ratio
N	Normality (Eq/L)
N_2	nitrogen gas
nBuLi	n-butyllithium
NaCl	sodium chloride
Na_2CO_3	sodium carbonate
$NaHCO_3$	sodium bicarbonate
NaH_2PO_4	sodium dihydrogen phosphate
$NaNO_2$	sodium nitrite
NaOH	sodium hydroxide
NaOtBu	sodium tert-butoxide
Na_2SO_4	sodium sulfate
$Na_2S_2O_3$	sodium thiosulfate
NH_3	ammonia, azane
NH_4Cl	ammonium chloride
NH_4OH	ammonium hydroxide
NMP	1-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance spectroscopy
OMe	methoxy
PO	per oral
+ve	positive
Ph	phenyl
PhMe	toluene
PMB	*p*-methoxybenzyl
$POCl_3$	phosphoryl chloride
ppm	parts per million
prep	preparative
psi	pounds per square inch
q	quartet
QD	once daily

QNMR	quantitative NMR
Rac	racemic
RBF	round-bottomed flask
RT, rt, or r.t.	room temperature
s	singlet
sat. or satd or sat'd	saturated
SFC	supercritical fluid chromatography
SIMes	1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene
SiO_2	silica
$SOCl_2$	thionyl chloride
t	triplet
TBDPS	tert-butyldiphenylsilyl
TBS	tert-butyldimethylsilyl
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl
t-BuOH	*tert*-butanol
TFA	triflouroacetic acid
THF	tetrahydrofuran
$Ti(OiPr)_4$	titanium isopropoxide
TLC	thin layer chromatography
TsOH	toluene sulfonic acid
UV	ultraviolet
v/v	volume per volume
wt%	weight percent

It is noted that when a percent (%) is used with regard to a liquid, it is a percent by volume with respect to the solution. When used with a solid, it is the percent with regard to the solid composition.

GENERAL SYNTHETIC SCHEMES

Unless otherwise stated, starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich

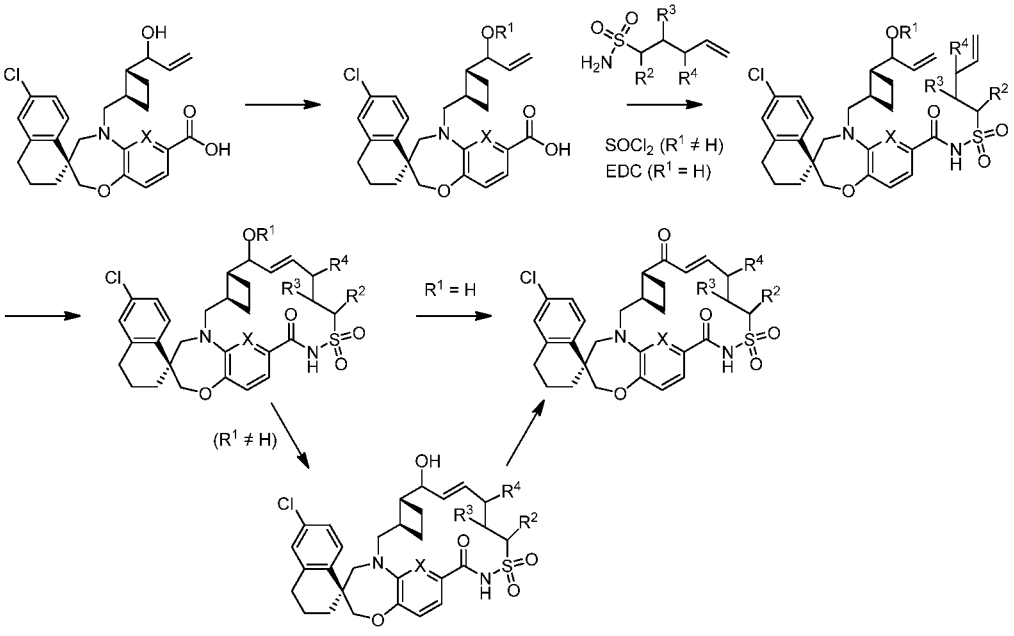
Chemical Co., (Milwaukee, Wis.) or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition) and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989).

The starting materials for the following synthetic methods can be found in the General Methods and General Synthesis for Intermediates. The synthesis of some of the starting materials and the intermediates are disclosed in U.S. Patent No. 9,562,061 and PCT/US17/19336, respectively, herein incorporated by reference in their entireties for all purposes. These synthetic methods are merely illustrative of some methods by which the compounds of this invention can be synthesized, and various modifications to these methods can be made and will be suggested to one skilled in the art having referred to this disclosure. The starting materials and the intermediates, and the final products of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

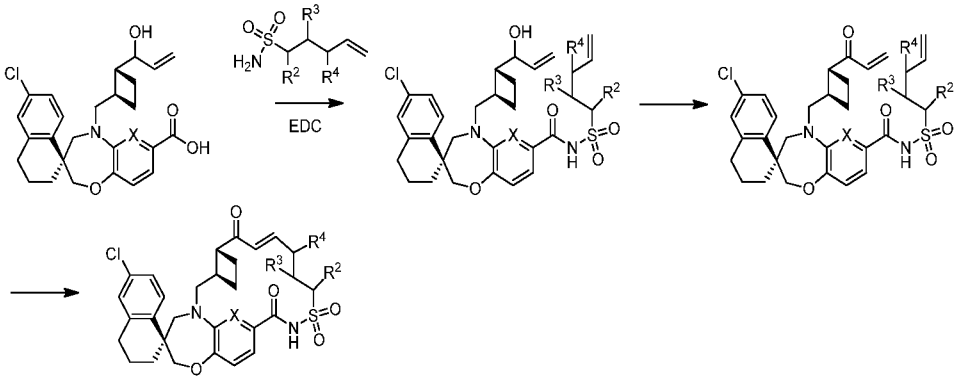
Unless specified to the contrary, the reactions described herein take place at atmospheric pressure over a temperature range from about –78 °C to about 150 °C, more preferably from about 0 °C to about 125 °C and most preferably at about room (or ambient) temperature, e.g., about 22 °C.

IUPAC names were generated using either ACD/Name v2015 or ChemBioDraw Ultra 12.

General Method 1: Enone Synthesis



General Method 2: Enone Synthesis



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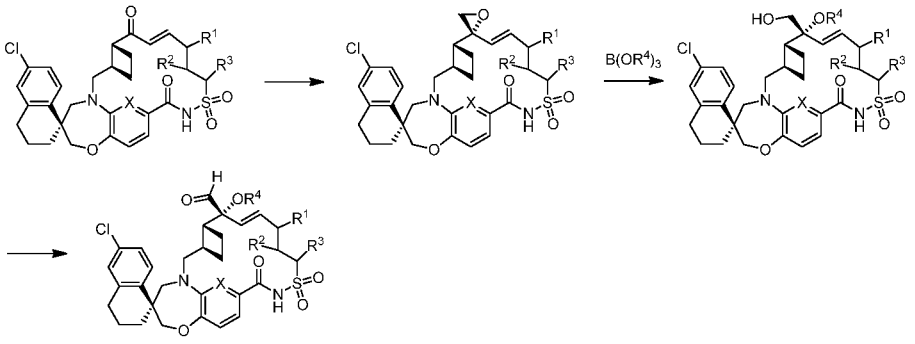
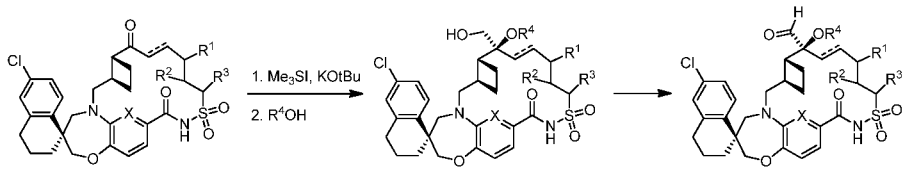
General Method 3: Conversion of Enone to Aldehyde via Epoxide



General Method 4: Conversion of Enone to Aldehyde via Epoxide



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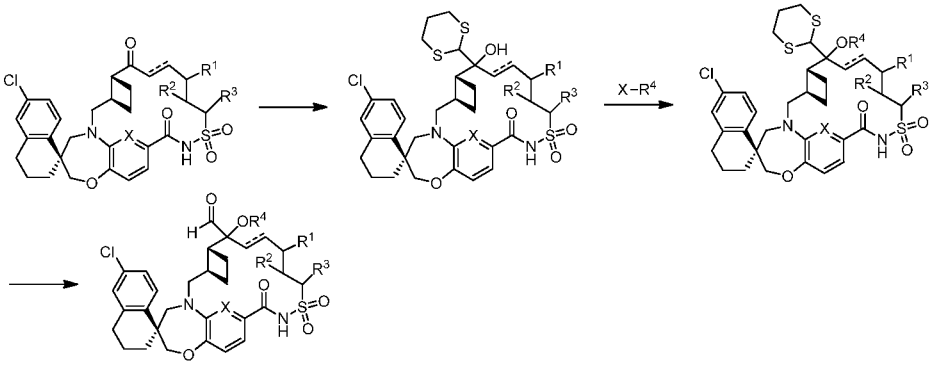
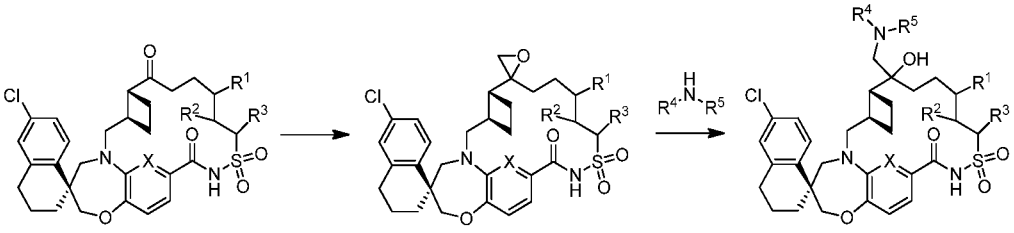
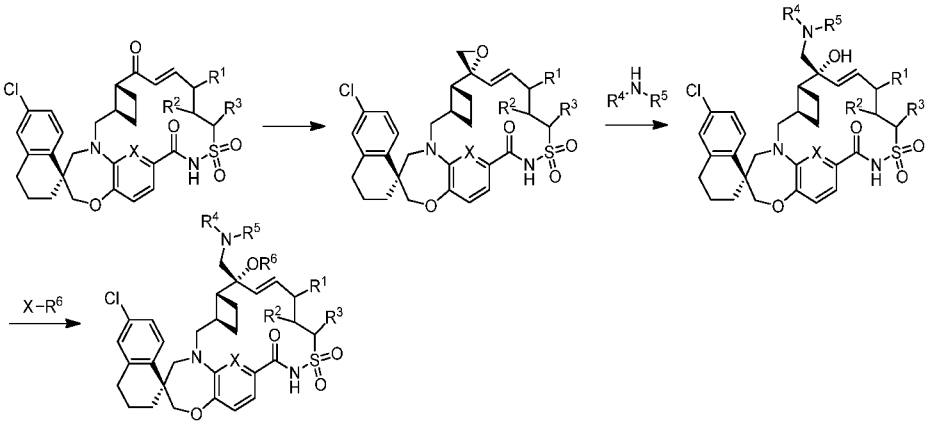
General Method 5: Conversion of Ketone to Aldehyde via Dithiane



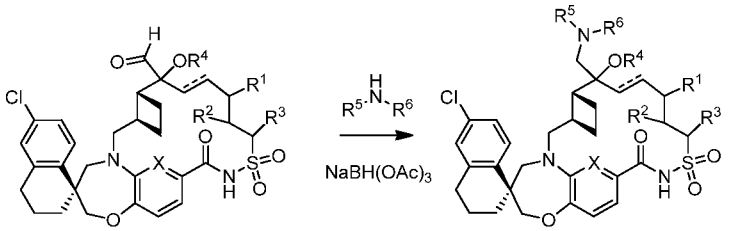
General Method 6: Conversion of Ketone to Amino Alcohol via Epoxide



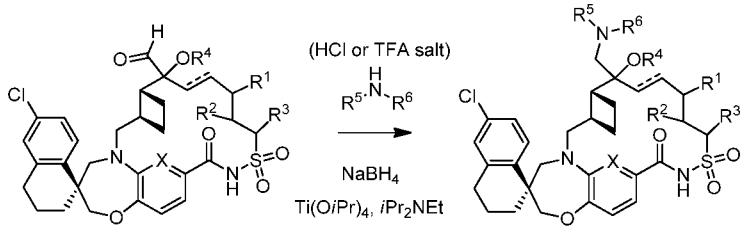
General Method 7: Conversion of Enone to Amino Ether



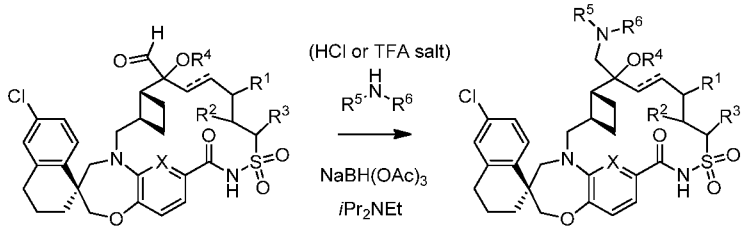
General Methods 8: Reductive Amination with $NaBH(OAc)_3$



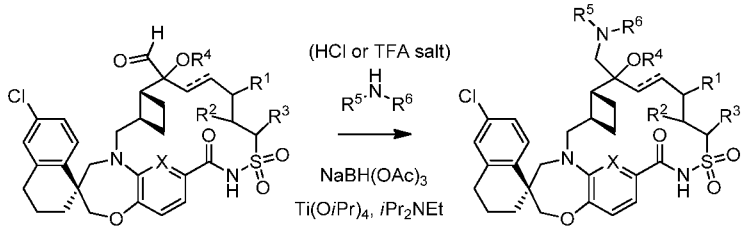
General Methods 9: Reductive Amination with $NaBH_4$, $Ti(OiPr)_4$, and Amine Salt



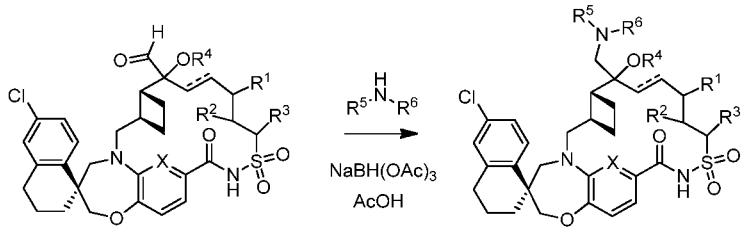
General Methods 10: Reductive Amination with $NaBH(OAc)_3$ and Amine Salt



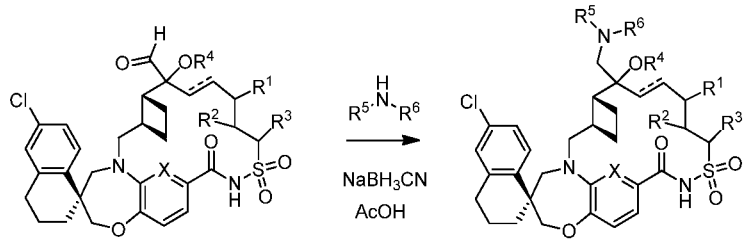
General Methods 11: Reductive Amination with $NaBH(OAc)_3$, $Ti(OiPr)_4$, and Amine Salt



General Methods 12: Reductive Amination with $NaBH(OAc)_3$ and AcOH



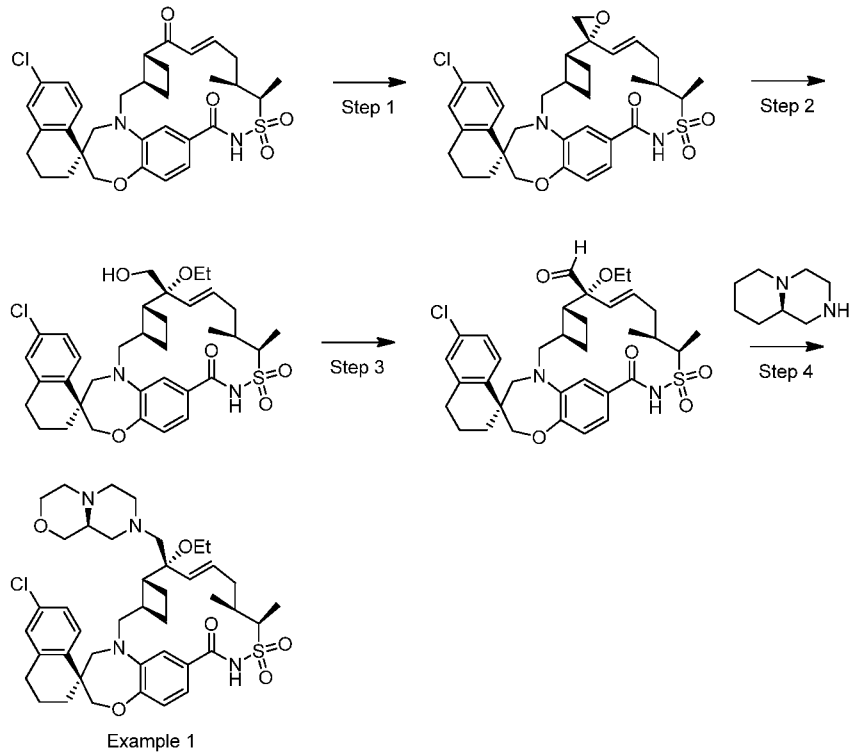
General Methods 13: Reductive Amination with $NaBH_3CN$ and AcOH



Example 1

(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

General Method 3 (Steps 1-3), General Method 7 (Step 1), General Method 8 (Step 4)



Example 1

Step 1: (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-7',2''-oxiran]-15'-one 13',13'-dioxide

A 250 mL 3-neck, equipped with a thermocouple, nitrogen inlet and septum, was charged with (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,7'H,15'H-spiro[naphthalene-1,22'[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7',15'-dione 13',13'-dioxide (10.05 g, 15.48 mmol) and trimethylsulfonium iodide (4.79 g, 23.47 mmol). Dimethyl sulfoxide (80 mL) and tetrahydrofuran (20 mL) were added and the reaction was cooled to 5 °C using an ice-water bath. The reaction was treated with 1 M potassium t-butoxide in THF (39.0 mL, 39.0 mmol) via syringe over a period of 20 min. The reaction was quenched with glacial acetic acid (2.20 mL, 38.1 mmol) and stirred for 1 min. The mixture was poured into isopropyl acetate (200 mL) and washed with water (200 mL). The aqueous layer was extracted with isopropyl acetate (100 mL) and the combined organic layers were washed with water (3 x 200 mL), brine (60 mL) and dried over Na_2SO_4. The solution was filtered and the filtrate was concentrated under reduced pressure. The residue was azeotrope with DCM (2 x 200 mL) then dissolved in DCM (40 mL). Heptane (400 mL) was added dropwise over a period of 1 h and the mixture was then stirred for 30 min. The solids were filtered and dried with nitrogen purge on the frit for 3 h to give 8.60 g of (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-7',2''-oxiran]-15'-one 13',13'-dioxide as a white solid. ^{1}H NMR (400 MHz, DICHLOROMETHANE-d_2) δ ppm 8.08 (s, 1 H), 7.72 (d, J=8.41 Hz, 1 H), 7.22 (d, J=0.98 Hz, 1 H), 7.19 (dd, J=8.41, 2.35 Hz, 1 H), 7.09 (d, J=2.15 Hz, 1 H), 6.83 – 6.95 (m, 2 H), 5.73 – 5.91 (m, 1 H), 5.60 (d, J=15.26 Hz, 1 H), 4.20 (q, J=7.24 Hz, 1 H), 4.01 – 4.14 (m, 2 H), 3.92 (dd, J=15.45, 4.50 Hz, 1 H), 3.73 (br

d, *J*=14.28 Hz, 1 H), 3.20 (d, *J*=14.28 Hz, 1 H), 2.96 (dd, *J*=15.55, 6.55 Hz, 1 H), 2.65 – 2.85 (m, 2 H), 2.47 (d, *J*=5.48 Hz, 1 H), 2.25 – 2.43 (m, 2 H), 1.73 – 2.08 (m, 9 H), 1.60 – 1.72 (m, 1 H), 1.33 – 1.44 (m, 4 H), 1.03 (br d, *J*=5.87 Hz, 3 H).

Step 2: (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-7'-(hydroxymethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

A 1 L 3-neck, equipped with a thermocouple, nitrogen adapter and septum, was charged with (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-7',2''-oxiran]-15'-one 13',13'-dioxide (10.22 g, 16.72 mmol) and 2-methyltetrahydrofuran (300 mL). Triethyl borate (50 mL, 291 mmol) was added via syringe and the reaction was placed on a heat block preheated to 65 °C. After 12 h the reaction was cooled to room temperature overnight. The reaction mixture was quenched with saturated $NaHCO_3$ (100 mL) and stirred for 10 min. The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and filtered. The filtrate was evaporated onto silica gel and purified by flash chromatography (Isco (330 gram)) eluting with 0.3% AcOH in EtOAc:0.3% AcOH in heptane (0:1 → 1:1) to afford 6.27 g of (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-7'-(hydroxymethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide. MS (ESI, +ve ion) *m/z* 657.3 $(M+1)^+$.

Step 3: (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide

A 250 mL 3-neck, equipped with a thermocouple, nitrogen adapter and septum, was charged with the starting (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-7'-(hydroxymethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (6.27 g, 7.54 mmol), DCM (50 mL) and dimethyl sulfoxide (20 mL). The solution was cooled (0 °C) in an ice bath, and N,N-diisopropylethylamine was added (6.6 mL, 37.8 mmol) followed by sulfur trioxide pyridine complex (3.02 g, 18.97 mmol), portion wise over 15 min. The ice bath was removed and allowed to warm to room temperature for 2 h. The reaction mixture was poured into isopropyl acetate (200 mL) and the solution was washed with water (200 mL). The aqueous layer was extracted with EtOAc (1 x 100 mL) and the combined organic layers were washed with 50% saturated NH_4Cl (2 x 100 mL), water (50 mL), brine (50 mL) and dried over Na_2SO_4. The solution was filtered and the filtrate was concentrated under reduced pressure to give a light-yellow solid. The solid was dissolved in EtOAc, evaporated onto silica gel and purified by flash chromatography (Isco (220 gram)) eluting with 0.3% AcOH in EtOAc:0.3% AcOH in heptane (0:1 → 1:1) to give 4.44 g of (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide as a white solid. MS (ESI, +ve ion) *m/z* 655.3 $(M+1)^+$.

Step 4: (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

Preparation of amine free base: To a room temperature suspension of (S)-octahydropiperazino[2,1-c]morpholine dihydrochloride (7.04 g, 32.7 mmol;

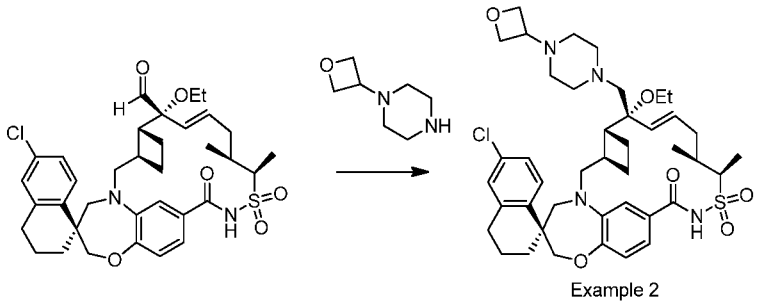
Synthonix, Wake Forest, NC) in DCM (100 mL) was added sodium methoxide (25 wt % solution in methanol, 15 mL, 65.6 mmol) and the reaction was stirred for 2 h. The solvent was removed under reduced pressure and the residue was stirred over EtOAc (100 mL) for 1 h. The solution was filtered and the filtrate was concentrated under reduced pressure to give (S)-octahydropyrazino[2,1-c][1,4]oxazine (4.33 g) as a light-yellow oil. ^{1}H NMR (400 MHz, DICHLOROMETHANE-d_2) δ ppm 3.70 – 3.82 (m, 1 H), 3.61 – 3.67 (m, 1 H), 3.52 – 3.60 (m, 1 H), 3.15 (t, *J*=10.47 Hz, 1 H), 2.79 – 2.93 (m, 2 H), 2.60 – 2.71 (m, 2 H), 2.55 (br d, *J*=11.54 Hz, 1 H), 2.27 – 2.39 (m, 2 H), 2.05 – 2.21 (m, 2 H).

To a room temperature solution of (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14] diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide (4.44 g, 6.51 mmol) in 1,2-dichloroethane (40 mL) was added a solution of (S)-octahydropyrazino[2,1-c][1,4]oxazine (2.91 g, 18.01 mmol) in 1,2-dichloroethane (5 mL) and the reaction was stirred for 2 h. To the reaction was added sodium triacetoxyborohydride (0.350 g, 1.651 mmol) was added as a solid. Additional sodium triacetoxyborohydride (0.350 g, 1.651 mmol) was added until the reaction was complete. The reaction was quenched with saturated NH_4Cl (40 mL) and the layers were separated. The aqueous layer was extracted with DCM (2x) and the combined organic layers were washed with 1 M KH_2PO_4 (40 mL). The organic layer was dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure and stored in the freezer. The residual material was dissolved in DCM, evaporated onto silica gel, and purified by flash chromatography (Isco (330 gram)) eluting with EtOAc:heptane:MeOH:DCM (0:1:0:0 → 3:2:0:0 → 0:0:1:49 → 0:0:3:47) to give 3.63 g (70%) of an off-white solid. The material was stirred over MeOH (15 mL) for 1 h. To the thick slurry was added MeOH (30 mL) to maintain good stirring. After another 1 h the solvent was removed under reduced pressure and the residue was dried in vacuo. The solid was dried under nitrogen purge/vacuum for 24 h to

give 3.10 g of (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide as a white solid. MS (ESI, +ve ion) *m/z* 781.3 $(M+1)^+$. ^{1}H NMR (400 MHz, DICHLOROMETHANE-d_2) δ ppm 7.72 (d, *J*=8.41 Hz, 1 H), 7.23 (s, 1 H), 7.17 (dd, *J*=8.41, 1.96 Hz, 1 H), 7.09 (d, *J*=1.96 Hz, 1 H), 6.89 (s, 2 H), 5.58 – 5.75 (m, 1 H), 5.43 (br d, *J*=15.85 Hz, 1 H), 4.15 (q, *J*=6.85 Hz, 1 H), 4.07 (s, 2 H), 4.01 (br d, *J*=15.45 Hz, 1 H), 3.74 – 3.82 (m, 1 H), 3.71 (br d, *J*=14.08 Hz, 1 H), 3.54 – 3.66 (m, 3 H), 3.43 – 3.52 (m, 1 H), 3.27 (d, *J*=14.28 Hz, 1 H), 3.17 (br t, *J*=10.37 Hz, 1 H), 2.89 – 3.03 (m, 2 H), 2.72 – 2.85 (m, 2 H), 2.58 – 2.71 (m, 2 H), 2.54 (m, 2 H), 2.48 (br d, *J*=14.28 Hz, 1 H), 2.20 – 2.40 (m, 5 H), 2.03 – 2.20 (m, 4 H), 1.65 – 2.00 (m, 6 H), 1.54 – 1.64 (m, 2 H), 1.41 (d, *J*=7.24 Hz, 3 H), 1.30 – 1.38 (m, 4 H), 1.01 (br d, *J*=5.67 Hz, 3 H).

Example 2

(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-11',12'-dimethyl-7'-((4-(3-oxetanyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide



Example 2

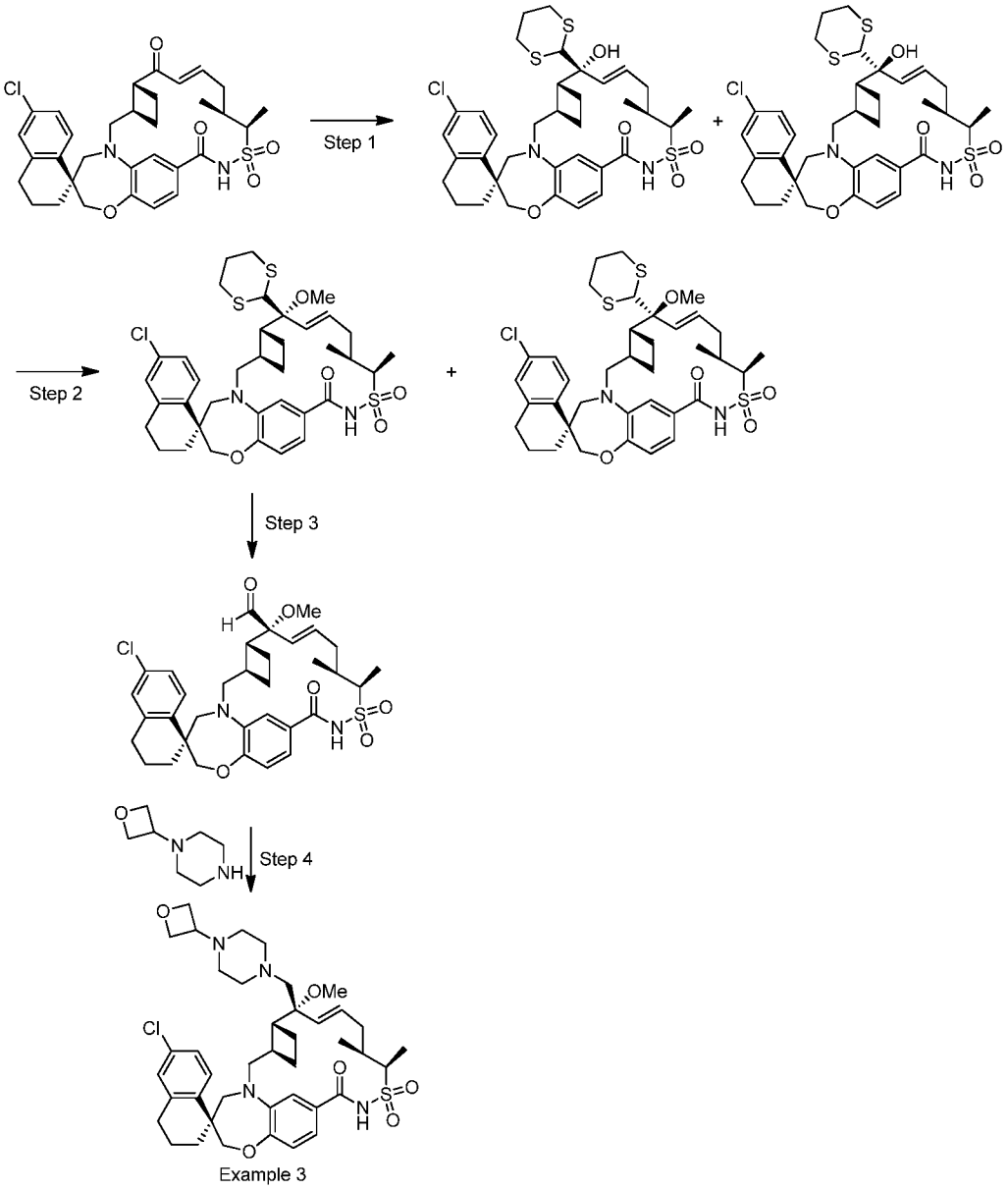
To a room temperature solution of (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-

[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide (0.050 g, 0.076 mmol) in 1,2-dichloroethane (1 mL) was added 1-(oxetan-3-yl)piperazine (0.100 mL, 0.823 mmol, Astatech, Inc., Bristol PA) via syringe and the reaction was stirred for 1 h. To the reaction was added sodium triacetoxyborohydride (0.050 g, 0.236 mmol) as a solid and the reaction was stirred overnight. The reaction was quenched with pH 7 buffer and the layers were separated. The aqueous layer was extracted with DCM (3x) and the combined organic layers were concentrated under reduced pressure. The residue was dissolved in MeOH and purified by reverse-phase HPLC (Gilson; Gemini-NX 10m C18 110 Å AXIA, 100 x 50 mm column) eluting with 0.1%TFA-H_2O:0.1%TFA CH_3CN (7:3 → 5:95). The fractions containing the desired product were combined, treated with pH 7 buffer (1 M KH_2PO_4/1 M K_2HPO_4; 5 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were washed with brine and dried over Na_2SO_4. The solution was filtered and concentrated under reduced pressure to give (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-11',12'-dimethyl-7'-((4-(3-oxetanyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (47 mg, 79%) as a white crystalline solid. MS (ESI, +ve ion) *m/z* 781.2 $(M+1)^+$. ^1H NMR (400 MHz, DICHLOROMETHANE-d_2) δ ppm 8.07 (br s, 1 H), 7.71 (d, *J*=8.41 Hz, 1 H), 7.23 (s, 1 H), 7.17 (dd, *J*=8.51, 2.25 Hz, 1 H), 7.08 (d, *J*=2.15 Hz, 1 H), 6.82 – 6.93 (m, 2 H), 5.61 – 5.78 (m, 1 H), 5.45 (br d, *J*=15.85 Hz, 1 H), 4.56 – 4.66 (m, 2 H), 4.44 – 4.54 (m, 2 H), 4.15 (br d, *J*=7.04 Hz, 1 H), 4.03 – 4.10 (m, 2 H), 3.99 (br d, *J*=14.67 Hz, 1 H), 3.70 (br d, *J*=14.28 Hz, 1 H), 3.61 (quin, *J*=7.24 Hz, 1 H), 3.35 – 3.52 (m, 2 H), 3.26 (d, *J*=14.28 Hz, 1 H), 2.95 (br dd, *J*=14.87, 9.98 Hz, 1 H), 2.72 – 2.85 (m, 2 H), 2.59 – 2.71 (m, 2 H), 2.46 – 2.57 (m, 4 H), 2.24 – 2.41 (m, 4 H), 2.02 – 2.19 (m, 4 H), 1.78 – 1.98 (m, 3 H), 1.70 (br s, 1 H), 1.57 (br d, *J*=6.26 Hz, 4 H), 1.29 – 1.45 (m, 7 H), 1.00 (br d, *J*=5.09 Hz, 3 H).

Example 3

(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-(3-oxetanyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

General Method 5 (Steps 1-3)



Step 1: (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-CHLORO-7'-(1,3-DITHIAN-2-YL)-7'-HYDROXY-11',12'-DIMETHYL-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[8,16,18,24]TETRAEN]-15'-ONE 13',13'-DIOXIDE AND (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-CHLORO-7'-(1,3-DITHIAN-2-YL)-7'-HYDROXY-11',12'-DIMETHYL-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[8,16,18,24]TETRAEN]-15'-ONE 13',13'-DIOXIDE

To a 250 mL round-bottomed flask was added 1,3-dithiane (4.79 g, 39.8 mmol) and THF (100 mL). The mixture was cooled to -78 °C and n-butyllithium (1.6 M solution in hexane, 22.5 mL, 36.1 mmol) was added over 8 min. The solution was stirred in the -78 °C bath for 30 min. In a separate 100 mL flask was added (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,7'H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7',15'-dione 13',13'-dioxide and THF (5 mL). To this was added lanthanum(III) chloride bis(lithium chloride) complex solution (0.6 M in THF, 60.1 mL, 36.1 mmol) and this was stirred for 5 min at room temperature. The solution was then cooled to -78 °C and added via cannula to the dithiane solution. After 2.5 h at -78 °C, the solution was treated with sat NH_4Cl and water. The pH of the solution was adjusted to pH = 4 with aqueous 10% citric acid and aqueous $NaHCO_3$. The solution was extracted with EtOAc and the combined extracts were filtered through Celite. The filtrate was washed with water and brine and then dried (Na_2SO_4) and concentrated to afford a mixture of (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide and (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-

7'-(1,3-dithian-2-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide as a brown oil which was carried on directly to next step. MS (ESI, +ve ion) *m/z* 717.5 $(M+H)^+$.

Step 2: (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-CHLORO-7'-(1,3-DITHIAN-2-YL)-7'-METHOXY-11',12'-DIMETHYL-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[8,16,18,24]TETRAEN]-15'-ONE 13',13'-DIOXIDE AND (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-CHLORO-7'-(1,3-DITHIAN-2-YL)-7'-METHOXY-11',12'-DIMETHYL-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[8,16,18,24]TETRAEN]-15'-ONE 13',13'-DIOXIDE

To a resealable vial was added the mixture of (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide and (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (6.81 g, 9.49 mmol) and THF (100 mL). The mixture was cooled to 0 °C and potassium bis(trimethylsilyl)amide (1 M in THF, 38.0 mL, 38.0 mmol) was added over 10 min. The solution was stirred at 0 °C for 5 min and then iodomethane (2.36 mL, 38.0 mmol) was added over 3 min. After 2.5 h at 0 °C, the solution was poured into saturated NH_4Cl and the pH was adjusted to 4 with 1 M citric acid. The solution was extracted with EtOAc and the combined extracts were washed with brine, dried (Na_2SO_4) and concentrated onto

silica. Purification by silica gel chromatography (0% to 35% EtOAc/heptane, both with 0.3% AcOH v/v, 330 g Redi-Sep Gold column) afforded: (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (1.66 g, 2.27 mmol, 24% yield). MS (ESI, +ve ion) *m/z* 731.5 $(M+H)^+$ and (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (4.69 g, 6.41 mmol, 68% yield). MS (ESI, +ve ion) *m/z* 731.5 $(M+H)^+$.

Step 3: (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide

To a 250 mL round-bottomed flask equipped with a reflux condenser was added (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (1.63 g, 2.23 mmol), acetonitrile (40 mL) and water (10 mL). The mixture was heated to 50 °C and calcium carbonate (1.12 g, 11.1 mmol) and iodomethane (1.38 mL, 22.3 mmol) were added. After 23 h at 50 °C, the solution was poured into sat NH_4Cl and water and then extracted with EtOAc. The combined extracts were washed with brine and then dried (Na_2SO_4) and concentrated onto silica. Purification by silica gel chromatography (0% to 40% EtOAc/heptane (both with 0.3% AcOH), Silicycle HP 120 g column) afforded (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,2

4]tetraene]-7'-carbaldehyde 13',13'-dioxide (1.34 g, 2.09 mmol, 94% yield) as a white solid. MS (ESI, +ve ion) *m/z* 641.3 $(M+H)^+$.

Step 4: (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-CHLORO-7'-METHOXY-11',12'-DIMETHYL-7'-((4-(3-OXETANYL)-1-PIPERAZINYL)METHYL)-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[8,16,18,24]TETRAEN]-15'-ONE 13',13'-DIOXIDE

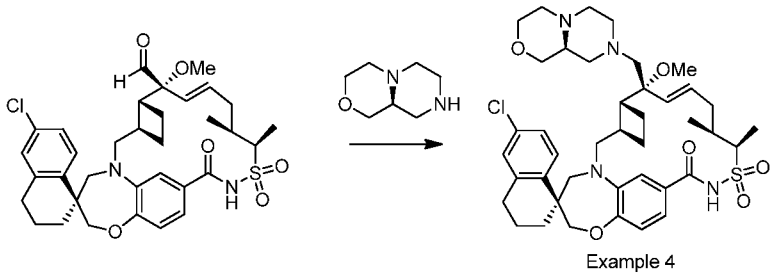
To a resealable vial was added (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide (0.135 g, 0.211 mmol), 1,2-dichloroethane (2.0 mL) and 1-(oxetan-3-yl)piperazine (0.090 g, 0.632 mmol, AstaTech, Inc.). The solution was stirred at room temperature for 1 h. To this solution was added sodium triacetoxyborohydride (0.011 g, 0.053 mmol). After stirring overnight at room temperature, additional portions of sodium triacetoxyborohydride (0.011 g, 0.053 mmol) were added until the reaction was complete. The reaction was carefully quenched with MeOH stirred for 1 h and then filtered for Prep-HPLC purification. The solution was purified by prep-HPLC (Column: Phenomenex Luna 5 μ C18, 100 Å, 150 x 20 mm; Solvent: A = water (0.1% TFA), B = (R) (0.1% TFA), 30 mL/min, 30% B to 100% B over 18 min then 2 min at 100% B) and the fractions containing product were treated with aqueous pH 7 buffer (KH_2PO_4/K_2HPO_4 based) and extracted with EtOAc. The combined extracts were washed with brine, and then dried (Na_2SO_4), filtered and concentrated to afford (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-(3-oxetanyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide as a white solid (0.101 g, 0.132 mmol, 63% yield). ^{1}H NMR (400 MHz, DICHLOROMETHANE-d_2) δ ppm 7.72 (d, *J*=9.8 Hz, 1 H), 7.25 (br s, 1 H), 7.16 (br d, *J*=8.6 Hz, 1 H), 7.09 (s, 1 H), 6.89 (s, 2 H), 5.62

(br s, 1 H), 5.37 (br d, *J*=14.9 Hz, 1 H), 4.56 – 4.66 (m, 2 H), 4.52 (br t, *J*=5.9 Hz, 2 H), 4.12 (br d, *J*=6.5 Hz, 1 H), 4.06 (s, 2 H), 3.98 (br d, *J*=14.9 Hz, 1 H), 3.70 (br d, *J*=14.1 Hz, 1 H), 3.40 – 3.52 (m, 1 H), 3.36 (s, 3 H), 3.19 – 3.30 (m, 1 H), 2.90 – 3.03 (m, 1 H), 2.64 – 2.85 (m, 4 H), 2.45 – 2.63 (m, 5 H), 2.26 – 2.41 (m, 4 H), 2.15 – 2.25 (m, 1 H), 2.02 – 2.15 (m, 3 H), 1.78 – 1.99 (m, 4 H), 1.66 – 1.76 (m, 1 H), 1.49 – 1.64 (m, 2 H), 1.40 (br d, *J*=7.2 Hz, 4 H), 1.01 (br d, *J*=5.7 Hz, 3 H). MS (ESI, +ve ion) *m/z* 767.3 $(M+H)^+$.

Example 4

(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-CHLORO-7'-((9AS)-HEXAHYDROPYRAZINO[2,1-C][1,4]OXAZIN-8(1H)-YLMETHYL)-7'-METHOXY-11',12'-DIMETHYL-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[8,16,18,24]TETRAEN]-15'-ONE 13',13'-DIOXIDE

General Method 9



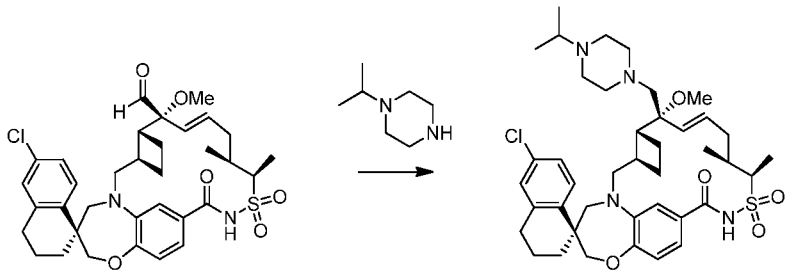
Example 4

To a 100 mL 3-neck flask was added (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide (0.486 g, 0.758 mmol), DCM (20 mL) and ethanol (8.0 mL). To this solution was added (9aS)-octahydropiperazino[2,1-c]morpholine dihydrochloride (1.96 g, 9.10 mmol) followed by N,N-diisopropylethylamine (4.0 mL, 22.7 mmol). To the solution was

added titanium(iv) isopropoxide (2.24 mL, 7.58 mmol). The solution was stirred at room temperature for 17 h. To this solution was added sodium borohydride (0.143 g, 3.79 mmol) in 3 portions. The reaction mixture was stirred at room temperature. After 18 h, additional sodium borohydride (35 mg) was added and stirring was continued at room temperature for an additional 24 h. The reaction was carefully quenched with sat. NH_4Cl and then diluted with aqueous pH 7 buffer (KH_2PO_4/K_2HPO_4 based), filtered through Celite, and extracted with EtOAc. The combined extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated to afford a white solid. The solid was purified by prep-HPLC (Column: Phenomenex Gemini C18 110 Å, 100 x 50 mm; Solvent: A = water (0.1% TFA), B = (R) (0.1% TFA), 100 mL/min, 10% B to 100% B over 11 min then 2 min at 100% B) and the fractions containing product were treated with aqueous pH 7 buffer (KH_2PO_4/K_2HPO_4 based), concentrated to remove the acetonitrile, and extracted with EtOAc. The combined extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated to afford (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide as a white solid (0.478 g, 0.622 mmol, 82% yield). ^{1}H NMR (400 MHz, DICHLOROMETHANE-d_2) δ ppm 7.72 (d, *J*=8.6 Hz, 1 H), 7.26 (s, 1 H), 7.17 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.09 (d, *J*=2.3 Hz, 1 H), 6.85 – 6.93 (m, 2 H), 5.57 – 5.68 (m, 1 H), 5.35 (s, 1 H), 4.08 – 4.17 (m, 1 H), 4.07 (s, 2 H), 3.96 – 4.04 (m, 1 H), 3.78 (br d, *J*=9.6 Hz, 1 H), 3.70 (br d, *J*=14.3 Hz, 1 H), 3.59 (br d, *J*=10.8 Hz, 2 H), 3.35 (s, 3 H), 3.25 (d, *J*=14.3 Hz, 1 H), 3.17 (br s, 1 H), 2.88 – 3.06 (m, 2 H), 2.72 – 2.81 (m, 2 H), 2.58 – 2.67 (m, 2 H), 2.45 – 2.54 (m, 3 H), 2.30 – 2.37 (m, 2 H), 2.17 – 2.27 (m, 3 H), 2.07 – 2.14 (m, 2 H), 2.03 – 2.07 (m, 1 H), 1.90 – 1.99 (m, 2 H), 1.81 – 1.90 (m, 2 H), 1.66 – 1.75 (m, 1 H), 1.48 – 1.65 (m, 4 H), 1.36 – 1.44 (m, 4 H), 1.02 (d, *J*=6.1 Hz, 3 H) MS (ESI, +ve ion) *m/z* 767.7 $(M+H)^+$.

Example 5

(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-CHLORO-7'-METHOXY-11',12'-DIMETHYL-7'-((4-(1-METHYLETHYL)-1-PIPERAZINYL)METHYL)-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[8,16,18,24]TETRAEN]-15'-ONE 13',13'-DIOXIDE



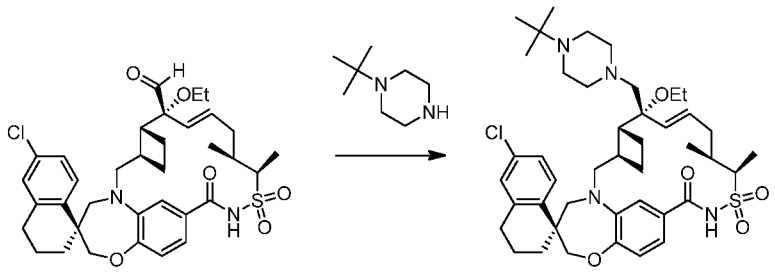
Example 5

To a resealable vial was added (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide (0.135 g, 0.211 mmol), 1,2-dichloroethane (2 mL) and 1-isopropylpiperazine (0.090 mL, 0.632 mmol, Across Organics). The solution was stirred at room temperature for 1 h. To this solution was added sodium triacetoxyborohydride (0.011 g, 0.053 mmol). After 2 h at room temperature, additional 0.25 eq. portions of sodium triacetoxyborohydride were added (4 total) until the reaction was complete. The reaction mixture was carefully quenched with MeOH, stirred for 1 h, and then filtered for Prep-HPLC purification. The solution was purified by prep-HPLC (Column: Phenomenex Luna C18, 100 Å, 150 x 21.20 mm; Solvent: A = water (0.1% TFA), B = (R) (0.1% TFA), 30 mL/min, 30% B to 100% B over 18 min then 2 min at 100% B) and the fractions containing product were treated with aqueous pH 7 buffer (KH_2PO_4/K_2HPO_4 based) and extracted with EtOAc. The combined extracts were washed with brine, and then dried (Na_2SO_4), filtered and concentrated to afford (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-(1-

methylethyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide as a white solid (0.0855 g, 0.113 mmol, 54% yield). ^{1}H NMR (400 MHz, DICHLOROMETHANE-d_2) δ ppm 7.76 (d, *J*=8.6 Hz, 1 H), 7.30 (s, 1 H), 7.20 (br d, *J*=8.4 Hz, 1 H), 7.13 (s, 1 H), 7.00 (d, *J*=8.2 Hz, 1 H), 6.92 (d, *J*=9.0 Hz, 1 H), 5.63 – 5.74 (m, 1 H), 5.49 (d, *J*=15.8 Hz, 1 H), 4.10 (s, 2 H), 3.96 – 4.05 (m, 2 H), 3.74 (br d, *J*=14.3 Hz, 1 H), 3.46 (s, 1 H), 3.38 – 3.43 (m, 1 H), 3.37 (s, 3 H), 3.30 (br d, *J*=14.3 Hz, 1 H), 2.96 – 3.04 (m, 2 H), 2.85 – 2.94 (m, 2 H), 2.77 – 2.84 (m, 2 H), 2.54 – 2.68 (m, 3 H), 2.36 – 2.43 (m, 1 H), 2.23 – 2.35 (m, 2 H), 2.14 – 2.23 (m, 2 H), 2.06 – 2.14 (m, 2 H), 1.83 – 2.03 (m, 4 H), 1.50 – 1.76 (m, 4 H), 1.35 – 1.47 (m, 10 H), 1.05 (d, *J*=6.7 Hz, 3 H). MS (ESI, +ve ion) *m/z* 753.2 $(M+H)^+$.

Example 6

(1S,3'R,6'R,7'R,8'E,11'S,12'R)-7'-((4-TERT-BUTYL-1-PIPERAZINYL)METHYL)-6-CHLORO-7'-ETHOXY-11',12'-DIMETHYL-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[8,16,18,24]TETRAEN]-15'-ONE 13',13'-DIOXIDE



Example 6

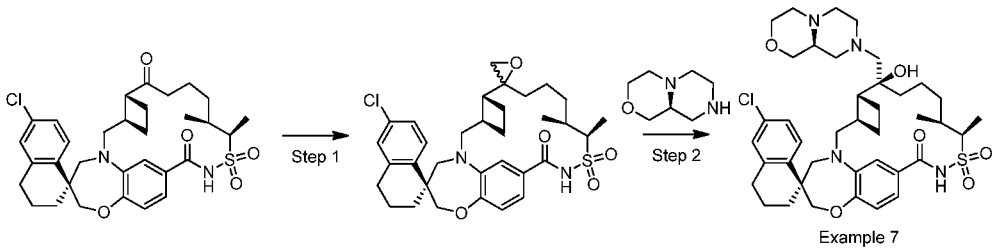
To a resealable vial was added (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide, 0.035 g, 0.053 mmol), 1,2-

dichloroethane (0.7 mL) and *N*-t-butylpiperazine (0.026 mL, 0.160 mmol, Oakwood Products, Inc.). The solution was stirred at room temperature for 30 min. To this solution was added sodium triacetoxyborohydride (2.83 mg, 0.013 mmol.). The reaction was stirred at room temperature. After 1 h, additional portions of sodium triacetoxyborohydride (2.83 mg, 0.013 mmol) were added every 1 h until the reaction was complete. The reaction was carefully quenched with MeOH, stirred for 30 min and then concentrated. Purification by silica gel chromatography (0% to 10% MeOH/CH_2Cl_2) afforded (1S,3'R,6'R,7'R,8'E,11'S,12'R)-7'-((4-tert-butyl-1-piperazinyl)methyl)-6-chloro-7'-ethoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide as a white solid (0.0284 g, 0.036 mmol, 68% yield). ^{1}H NMR (400 MHz, DICHLOROMETHANE-d_2) δ ppm 7.73 (d, *J*=8.6 Hz, 1 H), 7.31 (s, 1 H), 7.16 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.08 (d, *J*=2.2 Hz, 1 H), 7.02 (br d, *J*=8.0 Hz, 1 H), 6.84 (d, *J*=8.2 Hz, 1 H), 5.55 – 5.74 (m, 2 H), 3.96 – 4.10 (m, 3 H), 3.79 (br s, 1 H), 3.69 (br d, *J*=14.5 Hz, 1 H), 3.50 – 3.65 (m, 1 H), 3.34 – 3.45 (m, 1 H), 3.30 (d, *J*=14.3 Hz, 1 H), 2.94 – 3.04 (m, 1 H), 2.73 – 2.80 (m, 2 H), 2.58 – 2.68 (m, 3 H), 2.45 – 2.57 (m, 3 H), 2.29 – 2.35 (m, 1 H), 2.03 – 2.18 (m, 4 H), 1.90 – 1.98 (m, 2 H), 1.81 – 1.90 (m, 2 H), 1.55 – 1.70 (m, 3 H), 1.45 – 1.53 (m, 1 H), 1.34 – 1.44 (m, 1 H), 1.24 – 1.31 (m, 9 H), 1.17 – 1.24 (m, 9 H), 1.00 (d, *J*=6.8 Hz, 3 H). MS (ESI, +ve ion) *m/z* 781.3 $(M+H)^+$.

Example 7

(1S,3'R,6'R,7'S,11'S,12'R)-6-CHLORO-7'-((9AS)-HEXAHYDROPYRAZINO[2,1-C][1,4]OXAZIN-8(1H)-YLMETHYL)-7'-HYDROXY-11',12'-DIMETHYL-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[16,18,24]TRIEN]-15'-ONE 13',13'-DIOXIDE

General Method 6 (Steps 1-2)



Step 1: (1S,3'R,6'R,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',2''-oxiran]-15'-one 13',13'-dioxide

To a stirred solution of (1S,3'R,6'R,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,7'H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene]-7',15'-dione 13',13'-dioxide (100 mg, 0.167 mmol) and trimethylsulfoxonium iodide (38.6 mg, 0.175 mmol) in DMSO (1.5 mL) was added potassium hydroxide (33.0 mg, 0.501 mmol) at room temperature. The resulting mixture was stirred at room temperature for a period of 18 h. The mixture was poured into saturated ammonium chloride aqueous solution and extracted with EtOAc (2 X). The combined organics were dried over anhydrous sodium sulfate. The residue was subjected to combi-flash column chromatography on a 12 g ISCO gold column eluting with 10% to 100% EtOAc/hexanes to give (1S,3'R,6'R,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',2''-oxiran]-15'-one 13',13'-dioxide (72 mg, 0.117 mmol, 70% yield) as a mixture of diastereomers. MS (ESI, +ve ion) *m/z* 613.1 $(M+H)^+$.

Step 2: (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-

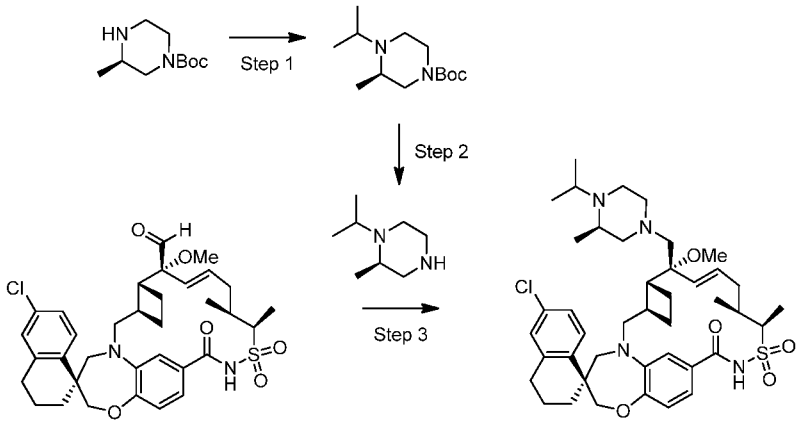
[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide

A mixture of (1S,3'R,6'R,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',2''-oxiran]-15'-one 13',13'-dioxide (840 mg, 1.37 mmol), (S)-octahydropyrazino[2,1-c][1,4]oxazine dihydrochloride (1.47 g, 6.85 mmol), and triethylamine (3.00 mL, 21.6 mmol) in EtOH (6.0 mL) in a sealed microwave reaction vessel was subjected to microwave reaction condition (24 h, 90 °C). The crude mixture was directly loaded onto a silica gel precolumn (25 g) and subjected to combi-flash column chromatography on a 12 g ISCO gold column eluting with 0% to 20 % MeOH/DCM to give an impure mixture of two epimeric beta-hydroxylamine products, which was subjected to separation by SFC (Column: MSA, Mobile Phase: 65:35 (A:B) isocratic, A: Liquid CO_2, B: methanol (20 mM NH_3), Flow Rate: 70 g/min, Column/Oven temp.: 40 °C, Detection: UV at 240 nm). The epimer first eluting on both the reverse-phase prep-HPLC and the SFC column was collected and subjected to combi-flash column chromatography on a 12 g ISCO gold column eluting with 0 to 20% MeOH/DCM to give (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide (340 mg, 0.45 mmol, 33% yield) as a white solid. ^{1}H NMR (400 MHz, DICHLOROMETHANE-d_2) δ 7.72 (d, *J*=8.61 Hz, 1H), 7.17 (dd, *J*=2.15, 8.41 Hz, 1H), 7.09 (d, *J*=2.15 Hz, 1H), 7.01 (s, 1H), 6.91-6.99 (m, 2H), 4.04-4.15 (m, 3H), 3.87 (br d, *J*=15.06 Hz, 1H), 3.78 (dd, *J*=2.93, 11.15 Hz, 1H), 3.69 (br d, *J*=14.28 Hz, 1H), 3.56-3.65 (m, 2H), 3.16-3.27 (m, 2H), 3.00 (br dd, *J*=8.71, 15.16 Hz, 1H), 2.87 (br d, *J*=9.98 Hz, 1H), 2.59-2.79 (m, 7H), 2.44-2.54 (m, 3H), 2.23-2.41 (m, 4H), 1.98-2.12 (m, 3H), 1.87-1.96 (m, 2H), 1.80-1.86

(m, 1H), 1.69-1.78 (m, 2H), 1.55 (br dd, *J*=9.29, 13.79 Hz, 3H), 1.20-1.44 (m, 9H), 0.98 (d, *J*=6.65 Hz, 3H). MS (ESI, +ve ion) *m/z* 755.3 $(M+H)^+$.

Example 8

(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-CHLORO-7'-METHOXY-11',12'-DIMETHYL-7'-(((3R)-3-METHYL-4-(1-METHYLETHYL)-1-PIPERAZINYL)METHYL)-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[8,16,18,24]TETRAEN]-15'-ONE 13',13'-DIOXIDE



Example 8

Step 1: (R)-TERT-BUTYL 4-ISOPROPYL-3-METHYLPIPERAZINE-1-CARBOXYLATE

A mixture of (R)-1-boc-3-methyl-piperazine (630 mg, 3.15 mmol) and acetone (3.0 mL, 40.9 mmol) in DCM (4.0 mL) was stirred for 10 min before sodium triacetoxyborohydride (1333 mg, 6.29 mmol) was added in one portion as a solid. The resulting mixture was stirred at room temperature for 2.5 days. MeOH (0.5 mL) was added to the reaction and the mixture was stirred for 5 min and then directly loaded onto a silica gel precolumn (25 g) and subjected to combi-flash column chromatography on a 24 g ISCO gold column eluting with 2% to 20% MeOH/DCM to give (R)-tert-butyl 4-isopropyl-3-methylpiperazine-1-carboxylate

(0.72 g, 2.97 mmol, 94% yield) as a colorless oil. ^{1}H NMR (400 MHz, DICHLOROMETHANE-d_2) δ 3.54-3.90 (m, 2H), 3.25 (td, *J*=6.41, 13.01 Hz, 1H), 3.02 (br s, 1H), 2.64-2.84 (m, 2H), 2.52-2.63 (m, 1H), 2.19-2.34 (m, 1H), 1.43 (s, 9H), 1.10 (d, *J*=6.65 Hz, 3H), 1.04 (d, *J*=6.26 Hz, 3H), 0.90 (d, *J*=6.65 Hz, 3H). MS (ESI, +ve ion) *m/z* 243.2 $(M+H)^+$.

Step 2: (R)-1-ISOPROPYL-2-METHYLPIPERAZINE BIS-TFA SALT

To a stirred solution of (R)-tert-butyl 4-isopropyl-3-methylpiperazine-1-carboxylate (670 mg, 2.76 mmol) in DCM (10 mL) was added trifluoroacetic acid (3.0 mL, 40 mmol) at room temperature. The resulting mixture was stirred at room temperature for 40 min. The volatiles were removed and the residue was subjected to high vacuum to give (R)-1-isopropyl-2-methylpiperazine bis-TFA salt as an off-white solid. ^{1}H NMR (400 MHz, DICHLOROMETHANE-d_2) δ 11.33-12.07 (m, 2H), 10.45-11.02 (m, 1H), 3.88-4.10 (m, 3H), 3.72-3.86 (m, 2H), 3.49-3.65 (m, 3H), 1.46 (dd, *J*=6.46, 12.91 Hz, 6H), 1.31 (d, *J*=6.65 Hz, 3H). MS (ESI, +ve ion) *m/z* 143.2 $(M+H)^+$.

Step 3: (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-Chloro-7'-methoxy-11',12'-dimethyl-7'-(((3R)-3-methyl-4-(1-methylethyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

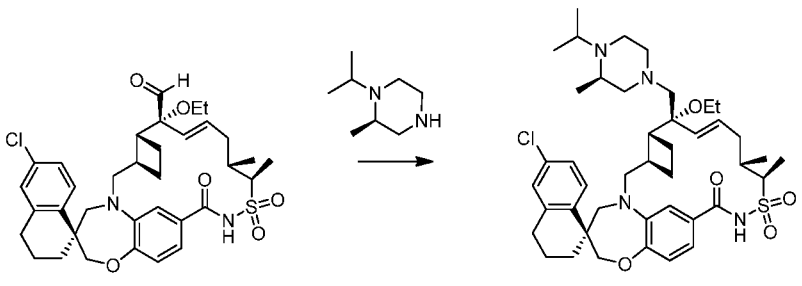
To a stirred mixture of (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide (20 mg, 0.031 mmol) and (R)-1-isopropyl-2-methylpiperazine bis-TFA salt (76.2 mg, 0.206 mmol) in DCM (1.5 mL) was added N,N-diisopropylethylamine (0.50 mL, 2.9 mmol). The resulting mixture was stirred at room temperature for 10 min before sodium triacetoxyborohydride (26.4 mg, 0.125 mmol) was added in one portion as a solid. The resulting mixture was stirred at room temperature for 25 h. The reaction

mixture was concentrated in vacuo and the residue was dissolved and taken up in MeOH and subjected to preparative reverse-phase HPLC (Gemini™ Prep C_{18} 10 µm column; Phenomenex, Torrance, CA; gradient elution of 35 to 90% MeCN in water, where both solvents contain 0.1% TFA, 15-min gradient in a 24 min method) to give, after lyophilization, (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-Chloro-7'-methoxy-11',12'-dimethyl-7'-(((3R)-3-methyl-4-(1-methylethyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (17.6 mg, 0.020 mmol, 64% yield) as a TFA salt as a white solid. ^{1}H NMR (400 MHz, DICHLOROMETHANE-d_2) δ 8.08 (br s, 1H), 7.71 (d, *J*=8.61 Hz, 1H), 7.11-7.20 (m, 2H), 7.09 (d, *J*=1.76 Hz, 1H), 6.90 (s, 2H), 5.78-5.96 (m, 1H), 5.47 (br d, *J*=15.65 Hz, 1H), 4.13-4.26 (m, 1H), 4.07 (s, 2H), 3.82-3.99 (m, 2H), 3.58-3.77 (m, 2H), 3.20-3.51 (m, 9H), 2.92-3.04 (m, 1H), 2.74-2.82 (m, 3H), 2.51-2.62 (m, 2H), 2.02-2.18 (m, 6H), 1.85-1.97 (m, 3H), 1.72-1.79 (m, 1H), 1.55-1.68 (m, 2H), 1.35-1.45 (m, 10H), 1.24 (d, *J*=6.85 Hz, 3H), 1.02 (d, *J*=6.65 Hz, 3H). MS (ESI, +ve ion) *m/z* 767.2 $(M+H)^+$.

Example 9

(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-CHLORO-7'-ETHOXY-11',12'-DIMETHYL-7'-(((3R)-3-METHYL-4-(1-METHYLETHYL)-1-PIPERAZINYL)METHYL)-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[8,16,18,24]TETRAEN]-15'-ONE 13',13'-DIOXIDE

General Method 10



Example 9

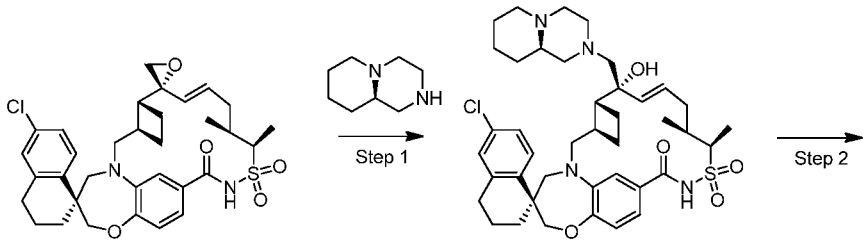
To an 1-dram vial was placed (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide (12 mg, 0.018 mmol) followed by a solution of (R)-1-isopropyl-2-methylpiperazine 2,2,2-trifluoroacetate (46.9 mg, 0.126 mmol) in DCM (1.5 mL) and N,N-diisopropylethylamine (0.60 mL, 3.5 mmol). The resulting mixture was stirred at room temperature for 10 min before sodium triacetoxyborohydride (16 mg, 0.073 mmol) was added in one portion as a solid. The resulting mixture was stirred at room temperature for 58 h. The reaction mixture was concentrated in vacuo and the residue was dissolved and taken up in MeOH and subjected to preparative reverse-phase HPLC (Gemini™ Prep C18 10 μm column; Phenomenex, Torrance, CA; gradient elution of 20% to 90% MeCN in water, where both solvents contain 0.1% TFA, 15-min gradient in a 24 min method) to give, after lyophilization, (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-Chloro-7'-ethoxy-11',12'-dimethyl-7'-(((3R)-3-methyl-4-(1-methylethyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (11.2 mg, 0.013 mmol, 70 % yield) as a TFA salt as a white solid. ^{1}H NMR (400 MHz, DICHLOROMETHANE-d_2) δ 8.05 (br s, 1H), 7.71 (d, *J*=8.61 Hz, 1H), 7.17 (dd, *J*=2.25, 8.51 Hz, 1H), 7.08-7.13 (m, 2H), 6.90 (s, 2H), 5.94-6.08 (m, 1H), 5.55-5.64 (m, 1H), 4.20-4.29 (m, 1H), 4.08 (s, 2H), 3.85-3.92 (m, 2H), 3.70-3.83 (m, 2H), 3.62-3.68 (m, 1H), 3.46-3.58 (m, 3H), 3.33 (br d, *J*=4.50 Hz, 2H), 3.26 (d, *J*=14.28 Hz, 1H), 2.99 (br dd, *J*=10.07, 14.57 Hz, 2H), 2.73-2.87 (m, 3H), 2.57 (br dd, *J*=7.92, 14.18 Hz, 2H), 2.11-2.18 (m, 3H), 2.06 (br d, *J*=13.89 Hz, 2H), 1.86-1.98 (m, 4H), 1.79 (br d, *J*=8.02 Hz, 1H), 1.67 (br d, *J*=4.89 Hz, 2H), 1.37-1.45 (m, 13H), 1.24 (d, *J*=6.65 Hz, 3H), 1.01 (d, *J*=6.65 Hz, 3H). MS (ESI, +ve ion) *m/z* 781.2 $(M+H)^+$.

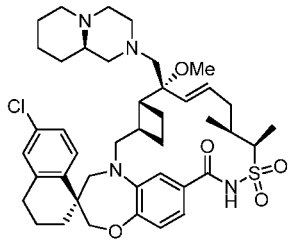
Example 10

(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-CHLORO-7'-METHOXY-11',12'-DIMETHYL-7'-((9AR)-OCTAHYDRO-2H-PYRIDO[1,2-A]PYRAZIN-2-

YLMETHYL)-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[8,16,18,24]TETRAEN]-15'-ONE 13',13'-DIOXIDE

General Method 7 (Steps 1-2)





Example 10

Step 1: (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-CHLORO-7'-HYDROXY-11',12'-DIMETHYL-7'-((9AR)-OCTAHYDRO-2H-PYRIDO[1,2-A]PYRAZIN-2-YLMETHYL)-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14] DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[8,16,18,24]TETRAEN]-15'-ONE 13',13'-DIOXIDE

Preparation of amine free base: To a 150 mL round bottomed flask was added (R)-octahydro-1H-pyrido[1,2-a]pyrazine dihydrochloride (5.0 g, 23.5 mmol, WuXi) and methanol (30 mL). To the solution at room temperature was added sodium methoxide (25 wt% solution in methanol, 14.0 mL, 58.6 mmol) over 2 min. The solution was stirred at room temperature for 10 min and then concentrated. The material was treated with 2-methyltetrahydrofuran to form a

suspension and then filtered. The filtrate was concentrated to form a viscous brown oil. The oil was treated with 2-methyltetrahydrofuran and heptane, filtered through a syringe filter and then concentrated to afford (R)-octahydro-1H-pyrido[1,2-a]pyrazine (3.4 g) as a brown semi-solid.

To a 250 mL 3-neck flask was added (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-7',2''-oxiran]-15'-one 13',13'-dioxide (4.75 g, 7.77 mmol), sodium tert-butoxide (1.49 g, 15.5 mmol), and 2-methyltetrahydrofuran (40 mL). To the solution was added (R)-octahydro-1H-pyrido[1,2-a]pyrazine (1.64 g, 11.7 mmol). The reaction mixture was then heated at 65 °C for 1 d. The solution was allowed to cool to room temperature and treated with pH 7 buffer (K_2HPO_4/KH_2PO_4 based). The solution was extracted with DCM (3x) and the combined extracts were washed with water and brine, dried over Na_2SO_4, and concentrated. The crude product, (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide, was carried on directly.

Step 2: (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-CHLORO-7'-METHOXY-11',12'-DIMETHYL-7'-((9AR)-OCTAHYDRO-2H-PYRIDO[1,2-A]PYRAZIN-2-YLMETHYL)-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[8,16,18,24]TETRAEN]-15'-ONE 13',13'-DIOXIDE

To a 250 mL flask containing (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo [14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

(5.8 g, 7.7 mmol) was added 2-methyltetrahydrofuran (80 mL). The solution was cooled to 0 °C and potassium bis(trimethylsilyl)amide (1 M in THF, 19.3 mL, 19.3 mmol) was added over 5 min. After stirring for 10 min at 0 °C, iodomethane (1.44 mL, 23.2 mmol) was added in one portion. The solution was stirred at 0 °C for 2 h and then additional potassium bis(trimethylsilyl)amide (4 mL) was added, stirred for 10 min and then additional iodomethane (0.48 mL) was added. The solution was stirred for 1 h at 0 °C and then aqueous pH 7 buffer (KH_2PO_4/K_2HPO_4 based) was added and the reaction mixture was allowed to warm to room temperature. The solution was extracted with DCM (3x) and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated onto silica. Purification by silica gel chromatography (10% to 60% EtOAc/heptane and then 5% to 10% MeOH/CH_2Cl_2) afforded (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide as an off-white solid (3.30 g, 4.31 mmol, 56% yield). ^{1}H NMR (400 MHz, DICHLOROMETHANE-d_2) δ ppm 7.72 (d, *J*=8.6 Hz, 1 H), 7.26 (d, *J*=1.4 Hz, 1 H), 7.17 (dd, *J*=8.6, 2.2 Hz, 1 H), 7.09 (d, *J*=2.0 Hz, 1 H), 6.92 – 6.99 (m, 1 H), 6.89 (d, *J*=8.0 Hz, 1 H), 5.64 (dt, *J*=15.7, 5.3 Hz, 1 H), 5.42 (br d, *J*=16.4 Hz, 1 H), 4.07 (s, 2 H), 4.03 (br d, *J*=7.2 Hz, 1 H), 3.98 (br d, *J*=14.9 Hz, 1 H), 3.70 (br d, *J*=14.3 Hz, 1 H), 3.34 (s, 3 H), 3.23 – 3.30 (m, 1 H), 3.06 – 3.22 (m, 2 H), 2.90 – 3.01 (m, 1 H), 2.74 – 2.81 (m, 2 H), 2.65 – 2.73 (m, 2 H), 2.52 – 2.62 (m, 4 H), 2.28 – 2.35 (m, 1 H), 2.16 – 2.26 (m, 2 H), 2.03 – 2.15 (m, 3 H), 1.81 – 1.99 (m, 6 H), 1.71 – 1.79 (m, 2 H), 1.57 – 1.71 (m, 4 H), 1.47 – 1.56 (m, 2 H), 1.34 – 1.44 (m, 5 H), 1.02 (d, *J*=6.7 Hz, 3 H). MS (ESI, +ve ion) *m/z* 765.3 $(M+H)^+$.

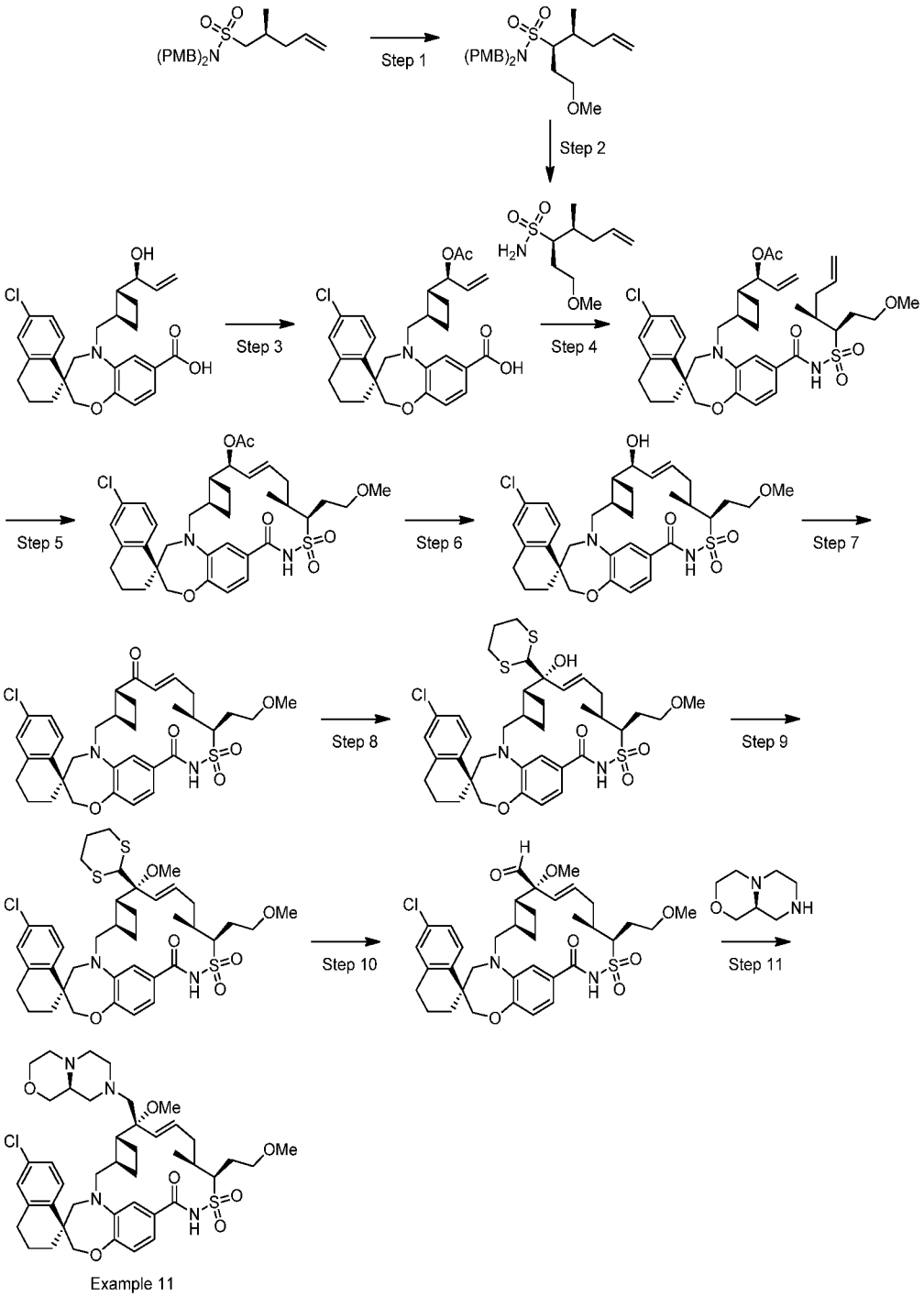
Example 11

(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-3,4-

dihydro-2H,15'H-spiro[naphthalene-1,22'-
[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]
pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

General Method 1 (Steps 3-7) and General Method 11 (Step 11)

5



Step 1: (3R,4S)-1-methoxy-N,N-bis(4-methoxybenzyl)-4-methylhept-6-ene-3-sulfonamide

A dry 2 L three neck flask with a thermo couple and magnetic stir bar under nitrogen was charged with (S)-N,N-bis(4-methoxybenzyl)-2-methylpent-4-ene-1-sulfonamide (54 g, 134 mmol) and 300 mL of dry toluene. Cooled solution to -76 °C internal temperature (acetone/dry ice bath). Added n-butyllithium solution (1.6 M in hexanes, 100 mL, 161 mmol) slowly via cannula under a positive pressure of nitrogen. The mixture was stired at -78 °C for 1 hour. Then 2-bromoethyl methyl ether (18.88 mL, 201 mmol) was slowly via syringe. After the addition, the -78 °C bath was replaced with an ice water bath. After a total of 105 minutes reaction time, the reaction was quenched with saturated ammonium chloride at 0 °C. The mixture was diluted with water and EtOAc and warmed to room temperature with stirring. The layers were separated and extracted with additional EtOAc. The combined organic layers were washed with water and brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude products were further separated to give 20.4 g of (3R,4S)-1-methoxy-N,N-bis(4-methoxybenzyl)-4-methylhept-6-ene-3-sulfonamide (44.2 mmol, 55 % yield). MS (ESI, +ve ion) *m/z* 484.0 $(M+Na)^+$.

Step 2: (3R,4S)-1-methoxy-4-methylhept-6-ene-3-sulfonamide

At 0 °C, trifluoroacetic acid (164 mL, 2210 mmol) was added dropwise via addition funnel to a solution of (3R,4S)-1-methoxy-N,N-bis(4-methoxybenzyl)-4-methylhept-6-ene-3-sulfonamide (20.4 g, 44.2 mmol) and anisole (48.0 mL, 442 mmol) in DCM (221 mL). The solution was allowed to come to room temperature and stirred overnight. The reaction was concentrated in vacuo. The remaining material was partitioned between DCM and saturated aqueous sodium bicarbonate. The layers were separated and the aqueous layer was extracted with DCM. The combined organic extracts were washed with saturated aqueous sodium chloride and dried over sodium sulfate. The solution was filtered and concentrated in vacuo to give the crude material. Purification by flash column chromatography on silica gel (eluted with 0% to 100% EtOAc in heptane) gave (3R,4S)-1-methoxy-4-methylhept-6-ene-3-sulfonamide (9.85 g,

44.5 mmol, 101% yield) as a light yellow oil. MS (ESI, +ve ion) *m/z* 243.9 $(M+Na)^+$.

Step 3: (S)-5-(((1R,2R)-2-((S)-1-acetoxyallyl)cyclobutyl)methyl)-6'-chloro-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylic acid

To a nitrogen inerted 3-neck 1 L flask equipped with a thermometer and a magnetic stir bar at room temperature was added 4-(dimethylamino) pyridine (0.821 g, 6.72 mmol), 2-methyltetrahydrofuran (80 mL), triethylamine (7.02 mL, 50.4 mmol), acetic anhydride (4.76 mL, 50.4 mmol), and a solution of (S)-6'-chloro-5-(((1R,2R)-2-((S)-1-hydroxyallyl)cyclobutyl)methyl)-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylic acid (15.72 g, 33.6 mmol) in 2-methyltetrahydrofuran (80 mL) was added via cannula over 20 min (internal temperature increased from 20 °C to 25 °C during the addition). The reaction mixture was stirred at room temperature for 1.5 h. Water (40 mL) was added (internal temperature increased from 23 °C to 26 °C) followed by 1 M Na_2HPO_4 (60 mL). Sodium hydroxide (1 M, 20 mL, 220 mmol) was added until the pH reached 9. The mixture was stirred at room temperature for 19 h and the pH was adjusted to 3 with 2 M HCl (80 mL). The mixture was diluted with PhMe (150 mL) and transferred to a separatory funnel. The aqueous layer was discarded and the organic phase was washed with water (75 mL), 20% brine (75 mL), and concentrated under reduced pressure. The concentrate was diluted with PhMe (100 mL) and the PhMe was removed under reduced pressure. This was repeated three times to give (S)-5-(((1R,2R)-2-((S)-1-acetoxyallyl)cyclobutyl)methyl)-6'-chloro-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylic acid as an orange oil that was used without further purification. MS (ESI, +ve ion) *m/z* 510.2 $(M+H)^+$.

Step 4: (S)-1-((1R,2R)-2-(((S)-6'-chloro-7-((((3R,4S)-1-methoxy-4-methylhept-6-en-3-yl)sulfonyl)carbamoyl)-3',4'-dihydro-2H,2'H-

spiro[benzo[b][1,4]oxazepine-3,1'-naphthalen]-5(4H)-yl)methyl)cyclobutyl)allyl acetate

To a 1 L 3-neck flask was charged (S)-5-(((1R,2R)-2-((S)-1-acetoxyallyl)cyclobutyl)methyl)-6'-chloro-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylic acid (28.73 g, 35.8 mmol) as a solution in toluene (228 mL). DMF (0.277 mL, 3.58 mmol) was added followed by slow addition of thionyl chloride (2.74 mL, 37.6 mmol) via syringe. The reaction was stirred at room temperature for 4 h and additional thionyl chloride (0.50 mL) was added and the reaction was stirred for 1 h. In a separate flask (3R,4S)-1-methoxy-4-methylhept-6-ene-3-sulfonamide (9.85 g, 42.5 mmol) and 4-(dimethylamino)pyridine (0.437 g, 3.58 mmol) were combined and azetroped by concentration in vacuo with PhMe (80 mL) and then taken up in 100 mL of PhMe. The resulting solution was added to the acid chloride solution described above via cannula. The solution was cooled in an ice bath for 10 min before triethylamine (17.41 mL, 125 mmol) was added dropwise via addition funnel. After the addition, the reaction was warmed to room temperature and stirred overnight. The reaction was quenched with saturated ammonium chloride. To the mixture was added 0.1 M aqueous HCl and then the mixture was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried with sodium sulfate, filtered, and concentrate in vacuo. Purification by flash column chromatography on silica gel (eluted with 0% to 100% EtOAc in heptane) gave (S)-1-((1R,2R)-2-(((S)-6'-chloro-7-((((3R,4S)-1-methoxy-4-methylhept-6-en-3-yl)sulfonyl)carbamoyl)-3',4'-dihydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalen]-5(4H)-yl)methyl)cyclobutyl)allyl acetate (28.11 g, 39.4 mmol) as an orange foam that was used in the next step without further purification. MS (ESI, +ve ion) *m/z* 713.0 $(M+H)^+$.

Step 5: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-12'-(2-methoxyethyl)-11'-methyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl acetate

To a 5 L reactor equipped with mechanical stirrer, thermo couple, nitrogen sparge tube, condenser, was charged 3.6 L of toluene. The PhMe was heated at 79 °C with sparging of nitrogen through the solution. In a separate flask, (S)-1-((1R,2R)-2-(((S)-6'-chloro-7-((((3R,4S)-1-methoxy-4-methylhept-6-en-3-yl)sulfonyl)carbamoyl)-3',4'-dihydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalen]-5(4H)-yl)methyl)cyclobutyl)allyl acetate (25.14 g, 32.0 mmol) was azetroped with 300 mL of toluene and then dissolved in 1.2 L PhMe which was added via syringe pump over 2 h. Simultaneously, 4 charges of Umicore M73 SIMes (4 x 238 mg) (Umicore AG & Co. KG, Precious Metals Chemistry, Rodenbacher Chaussee 4, 63457 Hanau-Wolfgang, Germany) was added as a slurry in 5 mL PhMe. Each charge was added at intervals of 40 min. After 4 h, the reaction was cooled to 30 °C and di(ethylene glycol) vinyl ether (0.350 mL, 2.56 mmol) was added and the solution was stirred overnight with the sparge replaced with a nitrogen inlet. The reactor was drained and the volume of the reaction was reduced to 1 L. SilaMetS Thiol (70 g) (SiliCycle Inc. 2500, Parc-Technologique Blvd Quebec City, Quebec, Canada) was added and the mixture was stirred overnight. The mixture was filtered and the SilaMetS Thiol was washed with EtOAc and the filtrate was concentrated. Purification by flash column chromatography on silica gel (330 g Gold Rf, eluted with 0% to 100 % EtOAc in heptane) gave (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-12'-(2-methoxyethyl)-11'-methyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl acetate (19.76 g, 28.8 mmol, 90% yield) as an orange oil. MS (ESI, +ve ion) *m/z* 685.0 $(M+H)^+$.

Step 6: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

Sodium methoxide (25% solution in methanol, 11.35 mL, 49.7 mmol) was added to a solution of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-12'-(2-methoxyethyl)-11'-methyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl acetate (19.76 g, 24.83 mmol) in toluene (100 mL) and methanol (20.00 mL) at room temperature. After 45 min, the reaction was quenched with citric acid (2 M aqueous solution, 37.2 mL, 74.5 mmol) and diluted with EtOAc and water. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with 2x water, saturated aqueous sodium chloride, and dried over sodium sulfate. The mixture was filtered and concentrated in vacuo and dried overnight to give (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide as an orange oil. MS (ESI, +ve ion) *m/z* 643.0 $(M+H)^+$.

Step 7: (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,7'H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7',15'-dione 13',13'-dioxide

To a 1 L flask containing (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (19.1 g, 29.7 mmol), prepared in the previous step, was added DCM (300 mL). The solution was cooled in an ice bath for 20 min. Dess-Martin periodinane (15.11 g, 35.6 mmol) was added in one portion and the reaction was stirred while cooled in the ice bath for 40 min. The reaction was removed from the ice bath and stirred for 1.5 h at room temperature. Sodium

thiosulfate was added followed by water and the mixture was stirred vigorously for 20 min. The reaction was diluted with saturated aqueous sodium bicarbonate and extracted with EtOAc (3x). The combined organic layers were washed with water and brine, dried with sodium sulfate, filtered, and concentrated. Purification by silica gel chromatography (eluted with 0% to 60% EtOAc in heptane) gave (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,7'H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7',15'-dione 13',13'-dioxide (14.29 g, 22.3 mmol, 75% yield) as a light yellow solid. MS (ESI, +ve ion) *m/z* 640.8 $(M+H)^+$.

Step 8: (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-hydroxy-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

To a 100 mL round-bottomed flask was added 1,3-dithiane (2.025 g, 16.84 mmol) in THF (42.1 mL). At -78 °C, n-butyllithium (2.5 M solution in hexane, 5.90 mL, 14.7 mmol) was added to the solution. The solution was stirred for 15 min and then (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,7'H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7',15'-dione 13',13'-dioxide (2.70 g, 4.21 mmol) in 10 mL of THF was added slowly. The mixture was stirred for 1 h and 10 mL of saturated ammonium chloride was added to quench the reaction. The mixture was diluted with 1 N HCl (20 mL) and extracted with EtOAc (3 x 40 mL). The organic extracts were washed with saturated NaCl (40 mL) and dried over $MgSO_4$. The solution was filtered and concentrated in vacuo. The material was purified by chromatography through a Redi-Sep pre-packed silica gel column (80 g), eluting with a gradient of 0% to 60% EtOAc (with 0.1% HOAc) in heptane to give (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-hydroxy-12'-

(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (1.6 g, 2.1 mmol, 50% yield). MS (ESI, +ve ion) *m/z* 761.1 $(M+H)^+$.

Step 9: (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

To a 100 mL round-bottomed flask was added (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-hydroxy-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (1.6 g, 2.1 mmol) and iodomethane (1.044 mL, 16.81 mmol) in THF (21 mL). At 0 °C, sodium hydride (0.504 g, 21.0 mmol) was added portion wise. The reaction Wwas stirred at room temperature for 5 h. The reaction mixture was diluted with saturated NH_4Cl (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with saturated NaCl (15 mL) and dried over $MgSO_4$. The solution was filtered and concentrated in vacuo. Purification by chromatography through a Redi-Sep pre-packed silica gel column (40 g), eluting with a gradient of 0% to 60% EtOAc (with 0.1% HOAc) in heptane gave (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (0.93 g, 1.2 mmol, 57% yield) as an off-white solid. MS (ESI, +ve ion) *m/z* 775.1 $(M+H)^+$.

Step 10: (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-

[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide

To a resealable vial was added (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (0.93 g, 1.2 mmol), acetonitrile (9.6 mL) and water (2.4 mL). To the mixture was added calcium carbonate (0.600 g, 6.00 mmol) and iodomethane (0.745 mL, 12.0 mmol). The mixture was heated at 45 °C overnight. The solution was poured into saturated NH_4Cl and water and then extracted with EtOAc. The combined extracts were washed with brine and then dried over Na_2SO_4 and concentrated. Purification by silica gel chromatography (eluted with 0% to 60% EtOAc in heptane (with 0.1% AcOH) gave (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide (0.70 g, 1.021 mmol, 85% yield) as a white solid. MS (ESI, +ve ion) *m/z* 685.1 $(M+H)^+$.

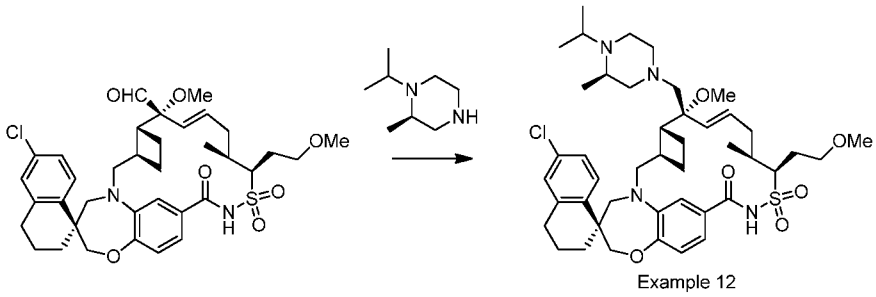
Step 11: (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

To a 100 mL round-bottomed flask was added (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide (450 mg, 0.657 mmol), (S)-octahydropyrazino[2,1-c][1,4]oxazine HCl salt (1130 mg, 5.25 mmol) and N,N-

diisopropylethylamine (2.341 mL, 13.13 mmol) in DCM (13.1 mL). Titanium(IV) isopropoxide (0.770 mL, 2.63 mmol) was added to the solution slowly. The reaction was stirred at room temperature overnight. Sodium triacetoxyborohydride (278 mg, 1.31 mmol) was added to the reaction portion wise and the mixture was stirred overnight. The reaction was diluted with saturated NaCl (20 mL). The white precipitate was removed by filtration through Celite. The filtrate was concentrated and diluted with 1 N HCl (20 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with saturated NaCl (50 mL) and dried over $MgSO_4$. The solution was filtered and concentrated in vacuo. The concentrate was absorbed onto a plug of silica gel and purified by chromatography through a Redi-Sep pre-packed silica gel column (40 g, with a layer of sodium bicarbonate on top). Elution with a gradient of 0% to 10% methanol in DCM gave (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (420 mg, 0.518 mmol, 79% yield) as a white solid. MS (ESI, +ve ion) *m/z* 811.0 $(M+H)^+$. 1H NMR (400 MHz, dichloromethane-d2) δ ppm 0.91 – 1.10 (m, 3 H), 1.33-1.72 (m, 10 H, with water residue), 1.81-1.97 (m, 5 H), 2.03 – 2.39 (m, 10 H), 2.41 – 2.69 (m, 6 H), 2.71 – 2.83 (m, 2 H), 2.90 – 3.08 (m, 2 H), 3.12 – 3.27 (m, 2 H), 3.33 (s, 3 H), 3.37 (s, 3 H), 3.53 – 3.83 (m, 6 H), 3.95-4.09 (m, 3 H), 4.11 – 4.22 (m, 1 H), 5.23 – 5.29 (m, 1 H), 5.55 – 5.62 (m, 1 H), 6.80 – 6.93 (m, 2 H), 7.09 (s, 1 H), 7.13 – 7.22 (m, 1 H), 7.30 (s, 1 H), 7.72 (d, J=8.41 Hz, 1 H).

Example 12

(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-7'-(((3R)-3-methyl-4-(1-methylethyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

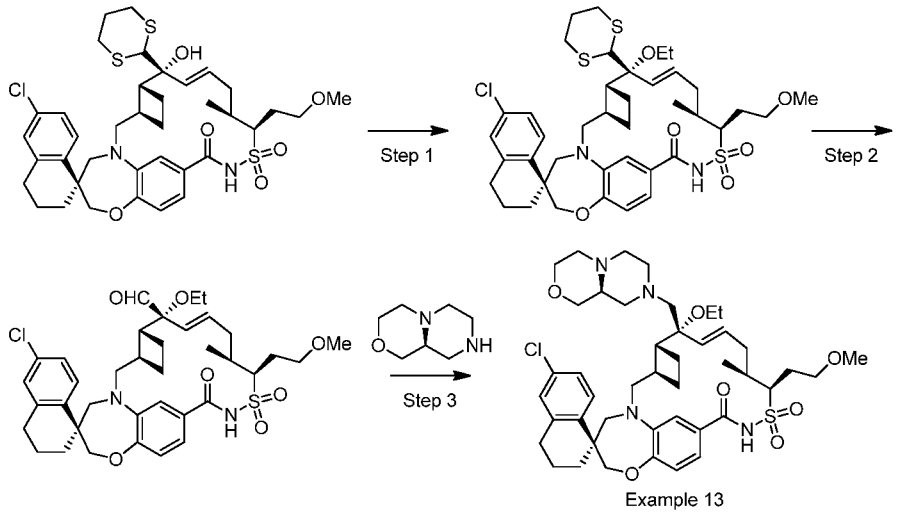


Example 12

To a 25 mL flask was added (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide (80 mg, 0.117 mmol), (R)-1-isopropyl-2-methylpiperazine bis(2,2,2-trifluoroacetate) (330 mg, 0.891 mmol), N,N-diisopropylethylamine (366 μL, 2.10 mmol) and titanium(IV) isopropoxide (137 μL, 0.467 mmol) in DCM (2335 μL). The solution was stirred at room temperature overnight. To this solution was added sodium triacetoxyborohydride (99 mg, 0.47 mmol). The reaction was stirred for 24 h. The reaction mixture was diluted with 1 N HCl (10 mL) and extracted with DCM (2 x 20 mL). The organic solvent was concentrated. The residue was purified by prep-HPLC to give (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-7'-(((3R)-3-methyl-4-(1-methylethyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide as a TFA salt. MS (ESI, +ve ion) *m/z* 811.2 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOH-d_4) δ ppm 1.06 (d, J=6.06 Hz, 3 H), 1.25-1.48 (m, 10 H), 1.49 – 2.30 (m, 12 H), 2.42 – 2.84 (m, 8 H), 2.94 – 3.27 (m, 4 H), 3.35 (s, 3 H), 3.42 (s, 4 H), 3.51-3.74 (m, 5 H), 3.91-4.10 (m, 3 H), 4.14 – 4.25 (m, 1 H), 5.35 (d, J=16.04 Hz, 1 H), 5.69 – 5.82 (m, 1 H), 6.86 – 6.94 (m, 1 H), 7.01 (dd, J=8.02, 1.76 Hz, 1 H), 7.10 (d, J=1.96 Hz, 1 H), 7.16 (dd, J=8.41, 2.15 Hz, 1 H), 7.26 (d, J=1.37 Hz, 1 H), 7.73 (d, J=8.61 Hz, 1 H).

Example 13

(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide



Example 13

Step 1: (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-ethoxy-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

To a 100 mL round-bottomed flask was added (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-hydroxy-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (0.62 g, 0.814 mmol) and iodoethane (0.655 mL, 8.14 mmol) in N, N-dimethylformamide (8.14 mL). At 0 °C, potassium bis(trimethylsilyl)amide (1 M in THF, 8.14 mL, 8.14 mmol) was added slowly. The reaction was stirred overnight. The reaction mixture was diluted with 1 N HCl (15 mL) and extracted with EtOAc (3 x 15 mL). The organic extract was washed

with saturated NaCl (15 mL) and dried over $MgSO_4$. The solution was filtered and concentrated in vacuo. The concentrate was absorbed onto a plug of silica gel and purified by chromatography through a 24 g ISCO gold column, eluted with a gradient of 0% to 40% EtOAc (with 0.1% of HOAc) in heptane, to provide (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-ethoxy-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (0.24 g, 0.304 mmol, 37% yield). MS (ESI, +ve ion) *m/z* 789.1 $(M+H)^+$.

Step 2: (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-12'-(2-methoxyethyl)-11'-methyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide

To a resealable vial was added (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-ethoxy-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (510 mg, 0.646 mmol), acetonitrile (5168 µL) and water (1292 µL). To the mixture was added calcium carbonate (323 mg, 3.23 mmol) and iodomethane (401 µL, 6.46 mmol). The mixture was heated at 45 °C overnight. The reaction was diluted with saturated NH_4Cl (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with saturated NaCl (20 mL) and dried over $MgSO_4$. The solution was filtered and concentrated in vacuo. The concentrate was absorbed onto a plug of silica gel and purified by chromatography through a Redi-Sep pre-packed silica gel column (40 g), eluting with a gradient of 0% to 60% EtOAc (with 0.1% of HOAc), to provide (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-12'-(2-methoxyethyl)-11'-methyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,2

4]tetraene]-7'-carbaldehyde 13',13'-dioxide (230 mg, 0.329 mmol, 50.9% yield) as a white solid. MS (ESI, +ve ion) *m/z* 699.1 $(M+H)^+$.

Step 3: (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

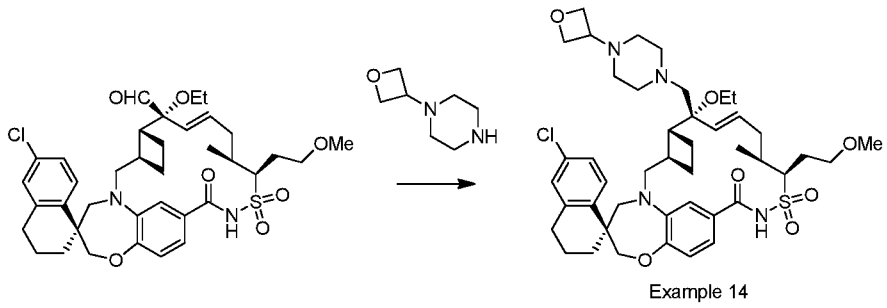
To a 50-mL round-bottomed flask was added (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-12'-(2-methoxyethyl)-11'-methyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide (150 mg, 0.215 mmol), (S)-octahydropyrazino[2,1-c][1,4]oxazine HCl salt (277 mg, 1.29 mmol) and N,N-diisopropylethylamine (574 μL, 3.22 mmol) in DCM (4290 μL). The reaction was stirred at room temperature overnight. Sodium triacetoxyborohydride (182 mg, 0.858 mmol) was added to the reaction mixture. The reaction was stirred for 8 h. The reaction mixture was diluted with 1 N HCl (20 mL) and extracted with DCM (2 x 20 mL). The organic layer was fully concentrated. The residue was further purified by prep-HPLC. The solution after pre-HPLC was washed with pH 7 solution and extracted with EtOAc (2 x 20 mL). The organic extract was washed with saturated NaCl (20 mL) and dried over $MgSO_4$. The solution was filtered and concentrated in vacuo to give (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide as a white solid. MS (ESI, +ve ion) *m/z* 825.2 $(M+H)^+$. ^1H NMR (400 MHz, dichloromethane-d2) δ ppm 1.01 (d, J=6.26 Hz, 3 H), 1.35 (t, J=6.85 Hz, 3 H), 1.44 – 1.74 (m, 7 H), 1.77 – 2.01 (m, 5 H), 2.04 – 2.38 (m, 9 H), 2.41 – 2.65 (m, 5 H), 2.70 – 2.83 (m, 2 H), 2.86 – 3.08 (m, 2 H), 3.27 (d, J=14.28 Hz, 1 H), 3.35 (s, 3 H), 3.40 – 3.49 (m, 1 H), 3.52-3.83 (m, 7 H),

3.99-4.10 (m, 3 H), 4.12 – 4.28 (m, 1 H), 5.35 – 5.42 (m, 1 H), 5.57 – 5.76 (m, 1 H), 6.85-6.92 (m, 2 H), 7.09 (d, J=2.15 Hz, 1 H), 7.13 – 7.20 (m, 1 H), 7.24 (s, 1 H), 7.72 (d, J=8.41 Hz, 1 H).

Example 14

(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-12'-(2-methoxyethyl)-11'-methyl-7'-((4-(3-oxetanyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

General Method 12



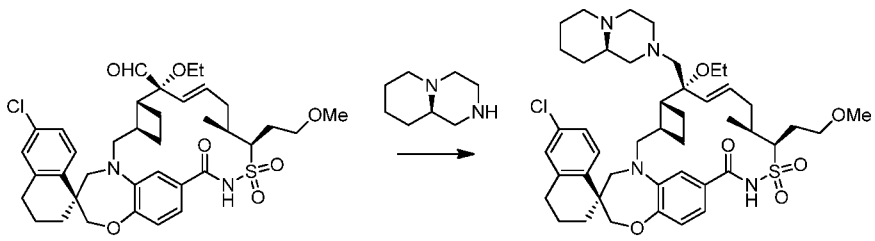
Example 14

To a 25 mL flask was added (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-12'-(2-methoxyethyl)-11'-methyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide (130 mg, 0.186 mmol) in DCM (3718 µL). To this solution was added 1-(oxetan-3-yl)piperazine (159 mg, 1.12 mmol) and a drop of acetic acid. The mixture was stirred for 8 h and sodium triacetoxyborohydride (158 mg, 0.744 mmol) was added. The reaction was stirred for 2 h and diluted with 1 N HCl (10 mL) and extracted with DCM (3 x 15 mL). The organic layer was concentrated. The concentrate was purified by prep-HPLC. The solution from prep-HPLC was washed with pH 7 buffer and extracted with EtOAc. The organic layer was concentrated to give

(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-12'-(2-methoxyethyl)-11'-methyl-7'-((4-(3-oxetanyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide as a white solid. MS (ESI, +ve ion) *m/z* 825.2 $(M+H)^+$. ^1H NMR (400 MHz, dichloromethane-d2) δ ppm 0.98 (br s, 3 H), 1.29 – 1.43 (m, 4 H), 1.47 – 2.24 (m, 12 H), 2.24 – 2.41 (m, 4 H), 2.45 – 2.84 (m, 9 H), 2.87 – 3.07 (m, 1 H), 3.27 (br d, J=14.09 Hz, 1 H), 3.34 (s, 3 H), 3.39 – 3.52 (m, 2 H), 3.57-3.76 (m, 4 H), 3.95-4.20 (m, 4 H), 4.45-4.55 (m, 2 H), 4.57-4.65 (m, 2 H), 5.38 – 5.51 (m, 1 H), 5.59 – 5.74 (m, 1 H), 6.89 (s, 2 H), 7.09 (d, J=1.96 Hz, 1 H), 7.13 – 7.19 (m, 1 H), 7.21 – 7.28 (m, 1 H), 7.72 (d, J=8.41 Hz, 1 H).

Example 15

(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-12'-(2-methoxyethyl)-11'-methyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide



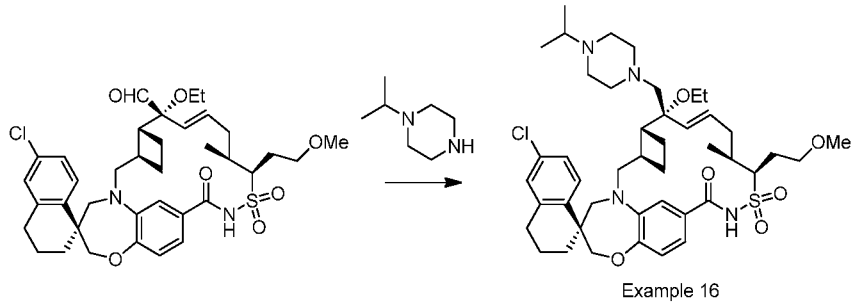
Example 15

To a 25 mL flask was added (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-12'-(2-methoxyethyl)-11'-methyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide (60 mg, 0.086 mmol) and (9ar)-octahydro-2h-pyrido[1,2-a]pyrazine (120 mg, 0.858 mmol) in DCM (1716 µL). A

drop of acetic acid was added. The solution was stirred at room temperature overnight. To this solution was added sodium triacetoxyborohydride (73 mg, 0.34 mmol). The reaction was stirred for 8 h and diluted with 1 N HCl (10 mL) and extracted with DCM (2 x 10 mL). The solvent was removed under reduced pressure. The concentrate was purified by prep-HPLC to give (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-12'-(2-methoxyethyl)-11'-methyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide as a TFA salt. MS (ESI, +ve ion) *m/z* 823.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOH-d_4) δ ppm 1.05 (d, J=6.46 Hz, 3 H), 1.37 (t, J=6.85 Hz, 3 H), 1.41 – 2.02 (m, 14 H), 2.04 – 2.26 (m, 5 H), 2.30-2.51 (m, 2 H), 2.51 – 2.87 (m, 6 H), 2.92 – 3.08 (m, 3 H), 3.11-3.26 (m, 2 H), 3.35-3.54 (m, 7 H), 3.60 – 3.78 (m, 4 H), 3.94-4.11 (m, 3 H), 4.18 – 4.29 (m, 1 H), 5.43 (d, J=16.04 Hz, 1 H), 5.67 – 5.89 (m, 1 H), 6.87 – 6.94 (m, 1 H), 6.95 – 7.03 (m, 1 H), 7.10 (d, J=1.96 Hz, 1 H), 7.14 – 7.19 (m, 1 H), 7.24 (d, J=1.56 Hz, 1 H), 7.73 (d, J=8.61 Hz, 1 H).

Example 16

(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-12'-(2-methoxyethyl)-11'-methyl-7'-((4-(1-methylethyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

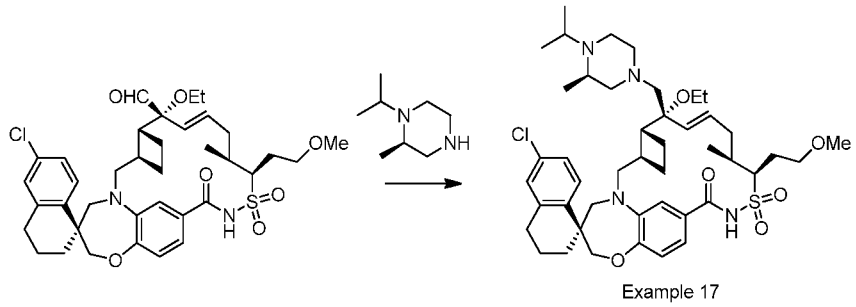


Example 16

To a 10 mL flask was added 1-isopropylpiperazine (123 µL, 0.858 mmol) and (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-12'-(2-methoxyethyl)-11'-methyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide (60 mg, 0.086 mmol) in DCM (1716 µL). A drop of acetic acid was added and the reaction was stirred overnight. Sodium triacetoxyborohydride (72.7 mg, 0.343 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 8 h. The reaction mixture was diluted with 1 N HCl (5 mL) and extracted with DCM (2 x 10 mL). The organic layer was concentrated. The concentrate was purified by prep-HPLC to give (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-12'-(2-methoxyethyl)-11'-methyl-7'-((4-(1-methylethyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide as a TFA salt. MS (ESI, +ve ion) *m/z* 811.2 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOH-d4) δ ppm 1.05 (d, J=6.46 Hz, 3 H), 1.29 – 1.47 (m, 10 H), 1.52 – 2.30 (m, 12 H), 2.51-2.87 (m, 8 H), 2.93 – 3.11 (m, 2 H), 3.38 (s, 4 H), 3.45 – 3.57 (m, 3 H), 3.59 – 3.78 (m, 4 H), 3.95-4.11 (m, 3 H), 4.20 – 4.33 (m, 1 H), 5.45 (d, J=15.85 Hz, 1 H), 5.77 – 5.91 (m, 1 H), 6.84 – 6.94 (m, 1 H), 6.96 – 7.02 (m, 1 H), 7.10 (d, J=1.96 Hz, 1 H), 7.16 (br d, J=8.41 Hz, 1 H), 7.23 (d, J=1.57 Hz, 1 H), 7.73 (d, J=8.41 Hz, 1 H).

Example 17

(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-12'-(2-methoxyethyl)-11'-methyl-7'-(((3R)-3-methyl-4-(1-methylethyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide



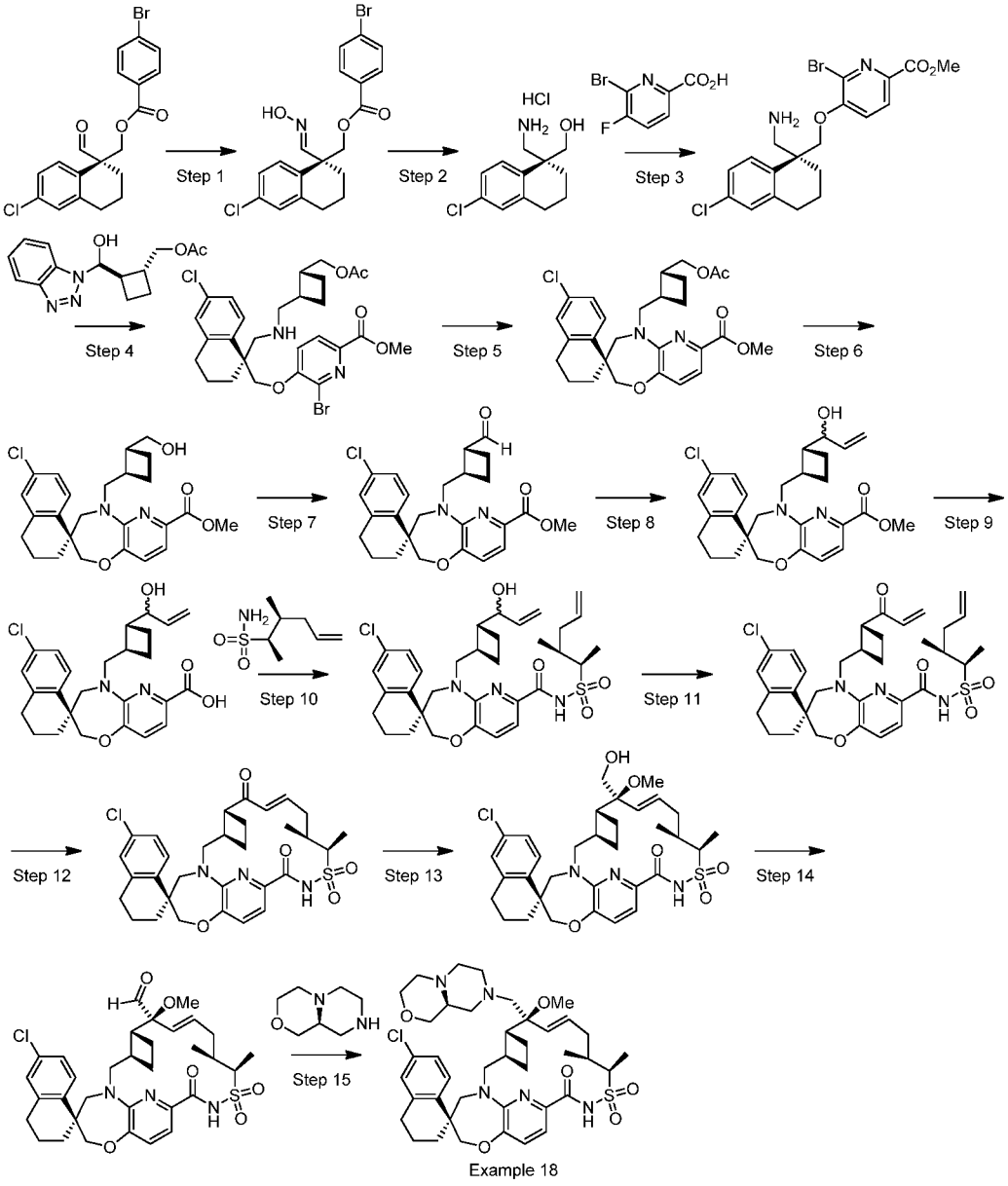
Example 17

To a 25 mL flask was added (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-12'-(2-methoxyethyl)-11'-methyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide (80 mg, 0.11 mmol), (R)-1-isopropyl-2-methylpiperazine bis(2,2,2-trifluoroacetate) (254 mg, 0.686 mmol), N,N-diisopropylethylamine (408 µL, 2.29 mmol) and titanium(IV) isopropoxide (134 µL, 0.458 mmol) in DCM (2288 µL). The solution was stirred at room temperature for 8 h. To this solution was added sodium triacetoxyborohydride (97 mg, 0.46 mmol). The reaction was stirred overnight. The reaction mixture was diluted with 1 N HCl (10 mL) and extracted with DCM (2 x 10 mL). The solvent was concentrated. The residue was purified by prep-HPLC to give (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-12'-(2-methoxyethyl)-11'-methyl-7'-(((3R)-3-methyl-4-(1-methylethyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide as a TFA salt. MS (ESI, +ve ion) *m/z* 825.4 $(M+H)^+$. ^1H NMR (400 MHz, MeOH-d_4) δ ppm 1.05 (d, J=6.46 Hz, 3 H), 1.21 – 1.49 (m, 13 H), 1.51 – 2.28 (m, 12 H), 2.37 – 2.87 (m, 8 H), 2.92 – 3.20 (m, 3 H), 3.36 – 3.57 (m, 7 H), 3.60 – 3.79 (m, 4 H), 3.97-4.07 (m, 3 H) 4.20 – 4.31 (m, 1 H), 5.43 (d, J=16.04 Hz, 1 H), 5.75 – 5.90 (m, 1 H), 6.87 – 6.94 (m, 1 H), 6.98-7.01 (m, 1 H), 7.10 (d, J=1.37 Hz, 1 H), 7.14-7.19 (m, 1 H), 7.24 (d, J=1.37 Hz, 1 H), 7.73 (d, J=8.61 Hz, 1 H).

Example 18

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

General Method 2 (Steps 10-12) and General Method 4 (Steps 13-14)



Step 1: (S,E)-(6-chloro-1-((hydroxyimino)methyl)-1,2,3,4-tetrahydronaphthalen-1-yl)methyl 4-bromobenzoate

To a stirred solution of (R)-(6-chloro-1-formyl-1,2,3,4-tetrahydronaphthalen-1-yl)methyl 4-bromobenzoate (425 g, 1042 mmol) in DCM (5100 mL) and MeOH (5100 mL) under a nitrogen atmosphere was added pyridine (337 mL, 4170 mmol) followed by hydroxylamine hydrochloride (145 g,

2085 mmol). The reaction mixture was stirred at room temperature for 3 h. The reaction was diluted with DCM (2.0 L) and the organic layer was washed with water (2.0 L). The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield (S,E)-(6-chloro-1-((hydroxyimino)methyl)-1,2,3,4-tetrahydronaphthalen-1-yl)methyl 4-bromobenzoate as yellow liquid. The material was used in the next step without further purification. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.85 – 7.80 (dd, J = 8.7, 2.1 Hz, 2H), 7.58 – 7.55 (m, 2H), 7.51 (s, 1H), 7.23 – 7.26 (m, 1H), 7.14 – 7.16 (m, 2H), 4.66 – 4.64 (d, J = 11.3 Hz, 1H), 4.56 – 4.53 (d, J = 11.2 Hz, 1H), 2.84 – 2.81 (t, J = 6.3 Hz, 2H), 2.14 – 2.02 (dddd, J = 14.8, 13.2, 7.1, 3.8 Hz, 2H), 1.96 – 1.83 (dddt, J = 13.9, 11.8, 5.9, 3.7 Hz, 2H).

Step 2: (S)-(1-(aminomethyl)-6-chloro-1,2,3,4-tetrahydronaphthalen-1-yl)methanol hydrochloride

(S,E)-(6-Chloro-1-((hydroxyimino)methyl)-1,2,3,4-tetrahydronaphthalen-1-yl)methyl 4-bromobenzoate (425 g, 1005 mmol), prepared in the previous step, was dissolved in THF (5160 mL) under a nitrogen atmosphere. The reaction mixture was cooled to 0 °C and lithium aluminum hydride (1.0 M in THF, 3519 mL, 3519 mmol) was added drop-wise. The ice-bath was removed and the reaction mixture was stirred at room temperature for 3 h. The reaction was cooled to 0 °C and water (160 mL) was added slowly, followed by 15% aqueous NaOH solution (160 mL) and water (500 mL). The mixture was allowed to stir for 10 min at room temperature and the reaction was filtered. The residual solids were washed with hot ethyl acetate (3 x 4.0 L). The combined filtrate was concentrated under reduced pressure to yield a yellow oil. The residue was dissolved in DCM (5160 mL) and the solution was cooled to 0 °C. A solution of HCl (4.0 M in dioxane, 65 mL) was added drop-wise and mixture was allowed to stir for 15 min at room temperature. The precipitate was collected by filtration. The solid was washed with ice-cold DCM (100 mL) and dried to afford (S)-(1-(aminomethyl)-6-chloro-1,2,3,4-tetrahydronaphthalen-1-yl)methanol hydrochloride (192 g, 72.8% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.38 – 7.36 (d, J = 8.2 Hz, 1H), 7.23 –

7.20 (m, 2H), 3.81 – 3.78 (m, 1H), 3.69 – 3.68 (dd, J = 10.9, 1.3 Hz, 1H), 3.48 – 3.45 (d, J = 13.1 Hz, 1H), 3.23 – 3.20 (d, J = 13.2 Hz, 1H), 2.83 – 2.81 (d, J = 6.3 Hz, 2H), 2.17 – 2.11 (m, 1H), 1.91 – 1.85 (m , 2H), 1.83 – 1.74 (m, 1H); exchangeable protons not observed.

Step 3: (S)-methyl 5-((1-(aminomethyl)-6-chloro-1,2,3,4-tetrahydronaphthalen-1-yl)methoxy)-6-bromopicolinate

To a stirred solution of (S)-(1-(aminomethyl)-6-chloro-1,2,3,4-tetrahydronaphthalen-1-yl)methanol hydrochloride (150 g, 572 mmol) was dissolved in dry DMSO (2250 mL) under a nitrogen atmosphere at room temperature. The solution was treated with 6-bromo-5-fluoropicolinic acid (151 g, 687 mmol) and the resulting solution was treated with potassium 2-methylpropan-2-olate (218 g, 1945 mmol) at room temperature. The reaction mixture was stirred for 2 h at room temperature and quenched by addition of acetic acid (~170 mL) at room temperature, followed by water (1.5 L) which resulted in precipitation of a solid. The solid was collected by filtration, washed with water (1.0 L), and dried. The solid was added to a pre-mixed solution of MeOH/H_2SO_4 (10:1, v/v, 5400 mL) and stirred at 80 °C for 3 h. The mixture was cooled to room temperature and solid K_2CO_3 (600 g) was slowly added to quench the sulfuric acid. The mixture was suspended in water (2 L) and ethyl acetate (2 L). The layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 2.5 L). The combined organic extracts were washed with brine (2.0 L), dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. Purification by column chromatography on silica gel (60-120 mesh, eluted with 0% to 5% MeOH in DCM) gave (S)-methyl 5-((1-(aminomethyl)-6-chloro-1,2,3,4-tetrahydronaphthalen-1-yl)methoxy)-6-bromopicolinate (170 g, 67.6 % yield) as off-white solid. MS (ESI, +ve ion) *m/z* 439.0 (M+1). ^{1}H NMR (400 MHz, Chloroform-d) δ 8.06 – 8.04 (dd, J = 8.4, 1.0 Hz, 1H), 7.51 – 7.49 (d, J = 8.4 Hz, 1H), 7.18 – 7.14 (m, 3H), 4.18 – 4.11 (m, 2H), 3.93 (s, 3H), 3.25 – 3.17 (m, 2H), 2.80 – 2.76 (m, 2H), 2.06 – 1.97 (m, 2H), 1.94 – 1.85 (tdd, J = 9.5, 6.7, 4.2 Hz, 2H); exchangeable protons not observed.

Step 4: methyl 5-(((S)-1-(((((1R,2R)-2-(acetoxymethyl)cyclobutyl)methyl)amino)methyl)-6-chloro-1,2,3,4-tetrahydronaphthalen-1-yl)methoxy)-6-bromopicolinate

To a stirred solution of (S)-methyl 5-((1-(aminomethyl)-6-chloro-1,2,3,4-tetrahydronaphthalen-1-yl)methoxy)-6-bromopicolinate (170 g, 387 mmol) in dry DCM (1.7 L) and acetic acid (1105 mL) under a nitrogen atmosphere was added ((1R,2S)-2-((S)-(1H-benzo[d][1,2,3]triazol-1-yl)(hydroxy)methyl)cyclobutyl)methyl acetate (128 g, 464 mmol) followed by sodium cyanoborohydride (31.6 g, 503 mmol) at 0 °C. The reaction was maintained at 0 °C for 2 h. The reaction was poured slowly into cold 10% sodium bicarbonate solution. The aqueous phase was extracted with ethyl acetate (2 x 2.0 L). The combined organic layer was washed with brine (1.0 L) and dried over sodium sulfate and concentrated under reduced pressure. Purification by column chromatography on silica gel (60-120 mesh, eluted with 2% to 5 % MeOH in DCM) gave methyl 5-(((S)-1-(((((1R,2R)-2-(acetoxymethyl)cyclobutyl)methyl)amino)methyl)-6-chloro-1,2,3,4-tetrahydronaphthalen-1-yl)methoxy)-6-bromopicolinate (149 g, 66.5 % yield) as yellow liquid. MS (ESI, +ve ion) *m/z* 579.1 (M+1). ^{1}H NMR (400 MHz, Chloroform-d) δ 8.08 – 8.06 (dt, J = 8.4, 1.3 Hz, 1H), 7.55 – 7.53 (dd, J = 8.3, 1.6 Hz, 1H), 7.19 – 7.13 (m, 3H), 4.13 (s, 2H), 4.10 – 4.00 (t, J = 2.3 Hz, 2H), 3.98 (d, J = 1.4 Hz, 3H), 3.05 – 2.98 (m, 2H), 2.79 – 2.78 (m, 2H), 2.69 – 2.58 (m, 2H), 2.18 – 2.11 (dd, J = 8.9, 4.9 Hz, 2H), 2.09 – 2.06 (dq, J = 9.7, 4.8, 3.1 Hz, 1H), 2.00 (t, J = 1.3 Hz, 3H), 1.97 – 1.82 (m, 6H), 1.65 – 1.61 (d, J = 9.2 Hz, 1H), 1.59 – 1.51 (q, J = 8.9 Hz, 1H).

Step 5: (S)-methyl 5'-(((1R,2R)-2-(acetoxymethyl)cyclobutyl)methyl)-6-chloro-3,4,4',5'-tetrahydro-2H,2'H-spiro[naphthalene-1,3'-pyrido[3,2-b][1,4]oxazepine]-7'-carboxylate

A solution of methyl 5-(((S)-1-(((((1R,2R)-2-(acetoxymethyl)cyclobutyl)methyl)amino)methyl)-6-chloro-1,2,3,4-

tetrahydronaphthalen-1-yl)methoxy)-6-bromopicolinate (36 g, 62.1 mmol) and N-ethyl-N-isopropylpropan-2-amine (161 mL, 933 mmol) in N-methyl-2-pyrrolidinone (360 mL) was stirred at 130 °C under a nitrogen atmosphere for 16 h. The reaction was cooled to room temperature and diluted with ethyl acetate (1.0 L). The mixture was washed with water (5 x 400 mL). The organic layer was dried with sodium sulfate, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (60-120 mesh, 0% to 10% EtOAc in hexane) gave (S)-methyl 5'-(((1R,2R)-2-(acetoxymethyl)cyclobutyl)methyl)-6-chloro-3,4,4',5'-tetrahydro-2H,2'H-spiro[naphthalene-1,3'-pyrido[3,2-b][1,4]oxazepine]-7'-carboxylate (16 g, 51.7 % yield) as yellow liquid. MS (ESI, +ve ion) *m/z* 499.1 (M+1). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.72 – 7.70 (d, J = 8.5 Hz, 1H), 7.46 – 7.44 (dd, J = 7.9, 1.1 Hz, 1H), 7.21 – 7.20 (dd, J = 8.5, 2.2 Hz, 1H), 7.18 – 7.11 (m, 2H), 4.18 – 4.15 (d, J = 12.2 Hz, 1H), 4.05 – 3.98 (m, 3H), 3.95 – 3.93 (d, J = 4.5 Hz, 1H), 3.91 – 3.89 (d, J = 1.0 Hz, 3H), 3.74 – 3.70 (d, J = 14.5 Hz, 1H), 3.42 – 3.32 (m, 2H), 2.79 – 2.76 (dt, J = 9.0, 5.1 Hz, 2H), 2.55 – 2.49 (dt, J = 15.5, 7.4 Hz, 2H), 1.98 – 1.85 (m, 8H), 1.76 – 1.74 (t, J = 9.4 Hz, 1H), 1.62 – 1.61 (d, J = 1.1 Hz, 1H), 1.50 – 1.49 (d, J = 1.1 Hz, 1H).

Step 6: (S)-methyl 6-chloro-5'-(((1R,2R)-2-(hydroxymethyl)cyclobutyl)methyl)-3,4,4',5'-tetrahydro-2H,2'H-spiro[naphthalene-1,3'-pyrido[3,2-b][1,4]oxazepine]-7'-carboxylate

To a stirred solution of (S)-methyl 5'-(((1R,2R)-2-(acetoxymethyl)cyclobutyl)methyl)-6-chloro-3,4,4',5'-tetrahydro-2H,2'H-spiro[naphthalene-1,3'-pyrido[3,2-b][1,4]oxazepine]-7'-carboxylate (68 g, 136 mmol) in THF (680 mL) and water (680 mL) was added lithium hydroxide monohydrate (22.87 g, 545 mmol) at room temperature. The reaction was allowed to stir at room temperature for 12 h. The reaction was concentrated under reduced pressure and the residue was taken up in MTBE (1.0 L), 10% citric acid monohydrate solution (500 mL) was added and the solution was stirred for 10 min. The layers were separated and the organic layer was washed with brine (500

mL), dried over sodium sulfate, and concentrated under reduced pressure. The concentrate was dissolved in dry methanol (600 mL) and cooled to 0 °C. Thionyl chloride (14.92 mL, 204 mmol) was added and the reaction was heated at 60 °C for 12 h. The reaction was cooled to 0 °C and quenched by slow addition of 10% sodium bicarbonate solution (500 mL) and extracted with ethyl acetate (2 x 500 mL). The combined organic layer was washed with brine (300 mL), dried over sodium sulfate, and concentrated under reduced pressure. The concentrate was suspended in acetonitrile (140 mL) and water (140 mL) was added. The mixture was stirred for 10 min. The solid was collected by filtration and dried to give (S)-methyl 6-chloro-5'-(((1R,2R)-2-(hydroxymethyl)cyclobutyl)methyl)-3,4,4',5'-tetrahydro-2H,2'H-spiro[naphthalene-1,3'-pyrido[3,2-b][1,4]oxazepine]-7'-carboxylate (58 g, 93% yield). MS (ESI, +ve ion) *m/z* 457.1 (M+1). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.73 – 7.72 (d, J = 8.5 Hz, 1H), 7.47 – 7.45 (d, J = 7.9 Hz, 1H), 7.21 – 7.19 (dd, J = 8.5, 2.3 Hz, 1H), 7.14 – 7.11 (m, 2H), 4.44 – 4.40 (m, 1H), 4.16 – 4.13 (d, J = 12.1 Hz, 1H), 4.06 – 4.03 (d, J = 12.1 Hz, 1H), 3.95 (s, 3H), 3.84 – 3.80 (d, J = 14.4 Hz, 1H), 3.75 – 3.68 (m, 1H), 3.57 – 3.56 (ddt, J = 14.1, 9.3, 4.2 Hz, 2H), 3.37 – 3.36 (d, J = 14.5 Hz, 1H), 2.96 – 2.90 (dd, J = 14.0, 9.1 Hz, 1H), 2.82 – 2.76 (m, 2H), 2.58 – 2.54 (m, 1H), 2.32 (td, J = 12.2, 10.4, 6.3 Hz, 1H), 2.02 – 1.95 (m, 3H), 1.88 – 1.83 (m, 2H), 1.67 – 1.55 (m, 2H), 1.49 – 1.43 (m, 1H).

Step 7: (S)-methyl 6-chloro-5'-(((1R,2R)-2-formylcyclobutyl)methyl)-3,4,4',5'-tetrahydro-2H,2'H-spiro[naphthalene-1,3'-pyrido[3,2-b][1,4]oxazepine]-7'-carboxylate

A 1 L 3-neck flask equipped with a mechanical stir bar and a temperature probe was charged with DCM (220 mL, 5V) followed by oxalyl chloride (10.16 mL, 116 mmol). The solution was cooled to -73 °C in a dry-ice acetone bath. DMSO (17.15 mL, 242 mmol) was added via syringe over 7 min (internal temperature increased from -74 °C to -60 °C during the addition). The mixture was held for 14 min and a solution of (S)-methyl 6-chloro-5'-(((1R,2R)-2-(hydroxymethyl)cyclobutyl)methyl)-3,4,4',5'-tetrahydro-2H,2'H-

spiro[naphthalene-1,3'-pyrido[3,2-b][1,4]oxazepine]-7'-carboxylate (44.2 g, 97 mmol) in DCM (220 mL, 5V) cooled in a dry-ice acetone bath was added via cannula over 12 min (internal temperature increased from -75 °C to -72 °C during the addition). The solution was stirred for 17 min and triethylamine (67.4 mL, 484 mmol) was added over 7 min (internal temperature increased from -76 °C to -65 °C during the addition). After the addition of the Et_3N, the reaction was held in the dry ice acetone bath for 5 min then warmed to 7 °C over 4 h and quenched with water (220 mL, 5V) (internal temperature increased from 7 °C to 15 °C during the quench). The mixture was transferred to a separatory funnel and the aqueous layer was discarded. The bottom layer was washed with saturated NH_4Cl (220 mL, 5V), 1:1 water:saturated $NaHCO_3$ (220 mL, 5V), and 1:1 water:brine (220 mL, 5V). The bottom organic layer was dried over $MgSO_4$, filtered through a fine frit, and concentrated under reduced pressure to give an off white foam. The foam was dissolved in 1:1 EtOAc/DCM (100 mL) and filtered through a 2 cm pad of silica (eluted with 400 mL of 1:1 EtOAc/DCM). The solution was concentrated under reduced pressure, diluted with PhMe (100 mL) and concentrated. This was repeated twice more and the product (S)-methyl 6-chloro-5'-(((1R,2R)-2-formylcyclobutyl)methyl)-3,4,4',5'-tetrahydro-2H,2'H-spiro[naphthalene-1,3'-pyrido[3,2-b][1,4]oxazepine]-7'-carboxylate was used without further purification. MS (ESI, +ve ion) *m/z* 454.9 $(M+H)^+$.

Step 8: (1S)-methyl 6-chloro-5'-(((1R,2R)-2-(1-hydroxyallyl)cyclobutyl)methyl)-3,4,4',5'-tetrahydro-2H,2'H-spiro[naphthalene-1,3'-pyrido[3,2-b][1,4]oxazepine]-7'-carboxylate

To a 2 L jacketed reactor was charged (-)-cinchonidine (5.69 g, 19.34 mmol) followed by PhMe (220 mL, 5V) and THF (220 mL, 5V). The solution was cooled to -23 °C (internal temperature) and zinc chloride (1.9 M in 2-methyltetrahydrofuran, 81 mL, 155 mmol) was added over 3 min (internal temperature increased from -23 °C to -19 °C during the addition). The solution was stirred for 5 min and vinylmagnesium chloride (1.6 M solution in THF, 206 mL, 329 mmol) was added via an addition funnel over 24 min (internal

temperature increased from -21 °C to -13 °C during the addition). The solution was stirred for 20 min (internal temperature decreased to -22 °C) and a solution of (S)-methyl 6-chloro-5'-(((1R,2R)-2-formylcyclobutyl)methyl)-3,4,4',5'-tetrahydro-2H,2'H-spiro[naphthalene-1,3'-pyrido[3,2-b][1,4]oxazepine]-7'-carboxylate, prepared in the previous step, in PhMe (220 mL, 5V) cooled in an ice-water bath was added via cannula over 8 min (internal temperature increased from -22 °C to -16 °C during the addition). The reaction was stirred at -20 °C for 1 h and warmed to 0 °C. After 45 min, the reaction was cooled to -8 °C and quenched with saturated NH_4Cl (350 mL, 8V). Water (88 mL, 2V) was added. Ammonium hydroxide (20 mL, 0.45V) was added and the solids dissolved. The aqueous phase was discarded. The organic phase was washed with saturated NH_4Cl (220 mL, 5 V), 1 M citric acid (4 x 88 mL, 2V), 1:1 water:brine (440 mL, 10V), dried over $MgSO_4$, filtered, and concentrated to give a yellow oil. MeOH (200 mL) was added and removed under reduced pressure. This was repeated a second time and the product (1S)-methyl 6-chloro-5'-(((1R,2R)-2-(1-hydroxyallyl)cyclobutyl)methyl)-3,4,4',5'-tetrahydro-2H,2'H-spiro[naphthalene-1,3'-pyrido[3,2-b][1,4]oxazepine]-7'-carboxylate was used without further purification as a mixture of diastereomers. MS (ESI, +ve ion) *m/z* 483.0 $(M+H)^+$.

Step 9: (1S)-6-chloro-5'-(((1R,2R)-2-(1-hydroxyallyl)cyclobutyl)methyl)-3,4,4',5'-tetrahydro-2H,2'H-spiro[naphthalene-1,3'-pyrido[3,2-b][1,4]oxazepine]-7'-carboxylic acid

To a 2 L jacketed reactor was charged a solution of (1S)-methyl 6-chloro-5'-(((1R,2R)-2-(1-hydroxyallyl)cyclobutyl)methyl)-3,4,4',5'-tetrahydro-2H,2'H-spiro[naphthalene-1,3'-pyrido[3,2-b][1,4]oxazepine]-7'-carboxylate, prepared in the previous step, in MeOH (234 mL, 5V) and THF (234 mL, 5V). Lithium hydroxide monohydrate (16.23 g, 387 mmol) was added and the reaction was stirred at room temperature for 17 h. Citric acid (1 M in water, 180 mL) was added followed by water (187 mL, 4V) and EtOAc (234 mL, 5V). All the solids dissolved. The mixture was drained from the reactor into a 3 L flask and the mixture was concentrated to half the original volume. EtOAc (234 mL, 5V) was

added and the mixture was transferred to a separatory funnel. The pH of the aqueous layer was 5. The aqueous layer was discarded. The organic layer was washed with 1:1 water:brine (235 mL, 5V), dried over $MgSO_4$, filtered, and concentrated to give 47.0 g of a yellow solid that was 79 wt% (1S)-6-chloro-5'-(((1R,2R)-2-(1-hydroxyallyl)cyclobutyl)methyl)-3,4,4',5'-tetrahydro-2H,2'H-spiro[naphthalene-1,3'-pyrido[3,2-b][1,4]oxazepine]-7'-carboxylic acid (37.1 g, 79 mmol, 82 % yield) and a mixture of diastereomers. MS (ESI, +ve ion) *m/z* 469.0 $(M+H)^+$.

Step 10: (1S)-6-chloro-5'-(((1R,2R)-2-(1-hydroxyallyl)cyclobutyl)methyl)-N-(((2R,3S)-3-methylhex-5-en-2-yl)sulfonyl)-3,4,4',5'-tetrahydro-2H,2'H-spiro[naphthalene-1,3'-pyrido[3,2-b][1,4]oxazepine]-7'-carboxamide

To a mixture of (1S)-6-chloro-5'-(((1R,2R)-2-(1-hydroxyallyl)cyclobutyl)methyl)-3,4,4',5'-tetrahydro-2H,2'H-spiro[naphthalene-1,3'-pyrido[3,2-b][1,4]oxazepine]-7'-carboxylic acid (34.7 g, 58.5 mmol), 4-(dimethylamino)pyridine (21.42 g, 175 mmol), and (2R,3S)-3-methylhex-5-ene-2-sulfonamide (21.41 g, 117 mmol) in a 500 mL 1-neck flask was added PhMe (100 mL). The PhMe was removed under reduced pressure and the concentrate was diluted with DCM (347 mL, 10V) and transferred to a 3-neck 1 L flask equipped with a temperature probe and a magnetic stirrer. Triethylamine (24.44 mL, 175 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide HCl (22.41 g, 117 mmol) were added and the reaction was stirred at room temperature. After 43 h, the reaction was diluted with water (240 mL, 7V) and transferred to a separatory funnel. The pH of the aqueous phase was adjusted to 4 with 1 M citric acid (240 mL, 7V) and the aqueous phase was discarded. The organic phase was washed with 1:1 brine:water (240 mL, 7V), dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography on silica gel (330 g silica, eluted with 50% to 100% DCM in heptane) gave (1S)-6-chloro-5'-(((1R,2R)-2-(1-hydroxyallyl)cyclobutyl)methyl)-N-(((2R,3S)-3-methylhex-5-en-2-yl)sulfonyl)-3,4,4',5'-tetrahydro-2H,2'H-spiro[naphthalene-1,3'-pyrido[3,2-b][1,4]oxazepine]-

7'-carboxamide (24.7 g, 39.3 mmol, 67 % yield) as a pale yellow foam and a mixture of diastereomers. MS (ESI, +ve ion) *m/z* 628.0 $(M+H)^+$.

Step 11: (S)-5'-(((1R,2R)-2-acryloylcyclobutyl)methyl)-6-chloro-N-(((2R,3S)-3-methylhex-5-en-2-yl)sulfonyl)-3,4,4',5'-tetrahydro-2H,2'H-spiro[naphthalene-1,3'-pyrido[3,2-b][1,4]oxazepine]-7'-carboxamide

A solution of (1S)-6-chloro-5'-(((1R,2R)-2-(1-hydroxyallyl)cyclobutyl)methyl)-N-(((2R,3S)-3-methylhex-5-en-2-yl)sulfonyl)-3,4,4',5'-tetrahydro-2H,2'H-spiro[naphthalene-1,3'-pyrido[3,2-b][1,4]oxazepine]-7'-carboxamide (2.82 g, 4.49 mmol) in DCM (28 mL, 10V) in a 100 mL 1-neck flask equipped with a temperature probe and magnetic stir bar was cooled to 2°C in an ice-water bath and Dess-Martin periodinane (2.094 g, 4.94 mmol) was added in one portion. The reaction was warmed to room temperature over 20 min and stirred at room temperature for 30 min. The solution was cooled to 2 °C in a water-ice bath and quenched with a solution of sodium thiosulfate (2.4 g) in water (8.4 mL, 3V) followed by saturated $NaHCO_3$ (20 mL, 7V). The internal temperature increased from 2 °C to 7 °C during the quench. The reaction was removed from the water-ice bath, warmed to room temperature, and stirred for 30 min. The mixture was transferred to a separatory funnel. The pH was adjusted to 7 with 1 M citric acid. The aqueous layer was discarded. The organic phase was washed with 1:1 water:brine (28 mL, 10V), dried over $MgSO_4$, filtered, and concentrated to give a yellow foam. The concentrate was dissolved in 10% EtOAc in DCM (~50 mL) and filtered through a 1 cm pad of silica gel (eluted with ~100 mL of 10% EtOAc in DCM). The filtrate was concentrated to give (S)-5'-(((1R,2R)-2-acryloylcyclobutyl)methyl)-6-chloro-N-(((2R,3S)-3-methylhex-5-en-2-yl)sulfonyl)-3,4,4',5'-tetrahydro-2H,2'H-spiro[naphthalene-1,3'-pyrido[3,2-b][1,4]oxazepine]-7'-carboxamide as a pale yellow foam that was used without further purification. MS (ESI, +ve ion) *m/z* 625.8 $(M+H)^+$. ^1H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.14 (d, J=6.85 Hz, 3H), 1.45 (d, J=7.04 Hz, 3H), 1.48 – 1.56 (m, 1H), 1.81 – 2.05 (m, 6H), 2.10 – 2.19 (m, 2H), 2.27 (q, J=8.80 Hz, 1H), 2.62 (qd, J=7.14, 2.45 Hz, 1H), 2.73 – 2.87 (m, 2H), 3.04 – 3.17 (m, 1H), 3.30 (q,

J=8.80 Hz, 1H), 3.36 – 3.43 (m, 1H), 3.43 – 3.47 (m, 1H), 3.78 (d, J=14.48 Hz, 1H), 3.89 – 4.07 (m, 3H), 4.20 (d, J=12.32 Hz, 1H), 5.07 – 5.15 (m, 2H), 5.74 – 5.87 (m, 2H), 6.15 – 6.32 (m, 2H), 7.12 (d, J=2.15 Hz, 1H), 7.18 – 7.22 (m, 2H), 7.58 (d, J=7.83 Hz, 1H), 7.69 (d, J=8.41 Hz, 1H), 9.90 (s, 1H).

Step 12: (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,7'H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7',15'-dione 13',13'-dioxide

To a 4-neck flask equipped with a magnetic stir bar, a temperature probe, and an air cooled condenser was charged PhMe (1.8 L, 250V). The solvent was heated to 80 °C and a gas dispersion tube was immersed into the solvent. Nitrogen gas was bubbled through the solvent via the gas dispersion tube. A solution of (S)-5'-(((1R,2R)-2-acryloylcyclobutyl)methyl)-6-chloro-N-(((2R,3S)-3-methylhex-5-en-2-yl)sulfonyl)-3,4,4',5'-tetrahydro-2H,2'H-spiro[naphthalene-1,3'-pyrido[3,2-b][1,4]oxazepine]-7'-carboxamide (8.93 g, 80 wt%, 11.41 mmol) in PhMe (65 mL) was added via an addition funnel over 2 h. During the addition of the diene, Umicore M73 SIMes (Umicore AG & Co. KG, Precious Metals Chemistry, Rodenbacher Chaussee 4, 63457 Hanau-Wolfgang, Germany) was added in four equal portions (total amount of catalyst was 0.346 g, 0.456 mmol) as a suspension in PhMe (4 mL) via syringe at: t = 0 min, t = 30 min, t = 60 min, and t = 90 min. After the addition of the diene was complete, the reaction was stirred for an additional 1 h at 80 °C. The reaction was cooled to room temperature and 2-(2-(vinyloxy)ethoxy)ethanol (0.125 mL, 0.913 mmol) and SilaMetS Thiol (SiliCycle Inc. 2500, Parc-Technologique Blvd Quebec City, Quebec, Canada) (7.71 g) were added. The mixture was stirred at room temperature for 18 h and the SilaMetS Thiol was removed by filtration and washed with EtOAc and concentrated to give a tan color solid. MeOH (~50 mL) was added and removed under reduced pressure. MeOH (107 mL, 15V) was added and the slurry was stirred at room temperature for 3 d and collected by filtration. The solid was washed with MeOH (1 x 40 mL) and dried on a frit under a vacuum with a

positive flow of nitrogen to give 6.39 g of an off white solid that was 66 wt% (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,7'H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7',15'-dione 13',13'-dioxide (4.22 g, 7.0 mmol, 62 % yield). MS (ESI, +ve ion) *m/z* 598.1 $(M+H)^+$.

Step 13: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(hydroxymethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

To a 3-neck flask equipped with temperature probe, septum, and nitrogen inlet was charged (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,7'H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7',15'-dione 13',13'-dioxide (6.33 g, 66 wt%, 6.98 mmol) and trimethylsulfonium iodide (2.138 g, 10.48 mmol). DMSO (35 mL) and THF (8.75 mL) were added and the mixture was stirred at room temperature for 20 min until the solids dissolved. The solution was cooled in an ice-water bath. When the internal temperature reached 6.5 °C, potassium tert-butoxide (1.0 M solution in THF, 17.46 mL, 17.46 mmol) was added slowly via syringe. After 40 min, a small amount of trimethylsulfonium iodide was added followed by potassium tert-butoxide (1 M solution in THF, 1.2 mL, 1.2 mmol). After 15 minutes, zinc(II) trifluoromethanesulfonate (0.5 M in MeOH, 84 mL, 41.9 mmol) was added over 5 min. After addition, the reaction was warmed to room temperature, stirred for 2 h and quenched with saturated ammonium chloride (~150 mL). Water and EtOAc were added. The aqueous phase was extracted with EtOAc (3 x). The combined organic extracts were concentrated. The concentrate was dissolved in EtOAc, washed with water (2 x), brine (1 x), dried over Na_2SO_4, filtered, and concentrated. The material was absorbed onto silica gel. Purification by flash column chromatography (330 g silica, eluted with 10% to 80% EtOAc (2%

AcOH) in heptane) gave 5.17 g of a light yellow solid that was 57 wt% (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(hydroxymethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (2.93 g, 4.55 mmol, 65 % yield). MS (ESI, +ve ion) *m/z* 644.0 $(M+H)^+$.

Step 14: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide

To a solution of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(hydroxymethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (79 wt%, 7.4 g, 9.07 mmol) in DCM (60 mL) and DMSO (30 mL) was added N,N-diisopropylethylamine (7.92 mL, 45.4 mmol). The solution was cooled in an ice water bath and pyridine-sulfur trioxide complex (3.61 g, 22.69 mmol) was added. After 40 min, the reaction was quench with saturated ammonium chloride and diluted water and EtOAc. The organic phase was washed with water. The combined aqueous phase was extracted with EtOAc (2 x). The combined organic phase was washed with 50% saturated ammonium chloride (2 x), brine, dried over Na_2SO_4, filtered, and concentrated to give (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide which was used without further purification. MS (ESI, +ve ion) *m/z* 641.9 $(M+H)^+$.

Step 15: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-11',12'-

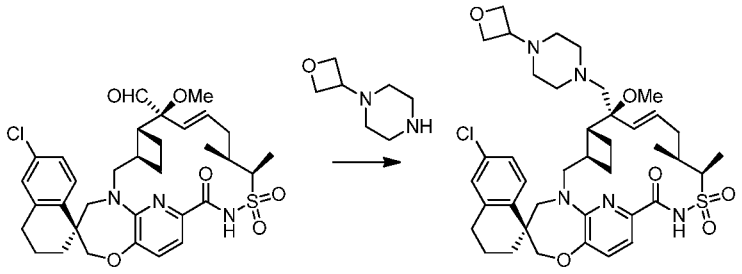
dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

To a solution of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide (5.28 g, 8.22 mmol) and (S)-octahydropyrazino[2,1-c][1,4]oxazine (3.51 g, 24.67 mmol) in DCM (82 mL) at room temperature was added acetic acid (0.475 mL, 8.22 mmol). The mixture was stirred at room temperature for 1 h and sodium triacetoxyborohydride (2.091 g, 9.87 mmol) was added slowly over 1 min. After 1 h, additional sodium triacetoxyborohydride (300 mg) was added. The reaction was stirred for 30 min and quenched with saturated NH_4Cl. The aqueous phase was extracted with DCM (3 x). The combined organic extracts were washed with saturated NH_4Cl (1 x), brine (1 x), dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (330 g silica, eluted with 0% to 10% MeOH in DCM) gave (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (6.02 g, 7.83 mmol, 95 % yield) as off-white solid. MS (ESI, +ve ion) *m/z* 768.2 $(M+H)^+$. ^1H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.17 (d, J=6.85 Hz, 3H), 1.46 (d, J=7.04 Hz, 3H), 1.48 – 1.63 (m, 4H), 1.68 – 2.09 (m, 8H), 2.19 (br d, J=17.22 Hz, 1H), 2.49 (br s, 3H), 2.33 (br s, 3H), 2.42 (br s, 1H), 2.55 – 2.70 (m, 2H), 2.77 – 3.04 (m, 6H), 3.08 (s, 3H), 3.15 (br s, 1H), 3.54 (br s, 1H), 3.66 (br s, 1H), 3.74 – 3.96 (m, 2H), 3.95 – 3.95 (m, 1H), 4.02 (d, J=12.32 Hz, 1H), 4.09 – 4.21 (m, 2H), 5.51 (br d, J=17.02 Hz, 1H), 5.64 (br d, J=16.82 Hz, 1H), 7.11 – 7.17 (m, 2H), 7.21 (dd, J=8.51, 2.25 Hz, 1H), 7.38 (d, J=7.82 Hz, 1H), 7.67 (d, J=8.61 Hz, 1 H), 9.12 (br s, 1H).

Example 19

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-(3-oxetanyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

General Method 13



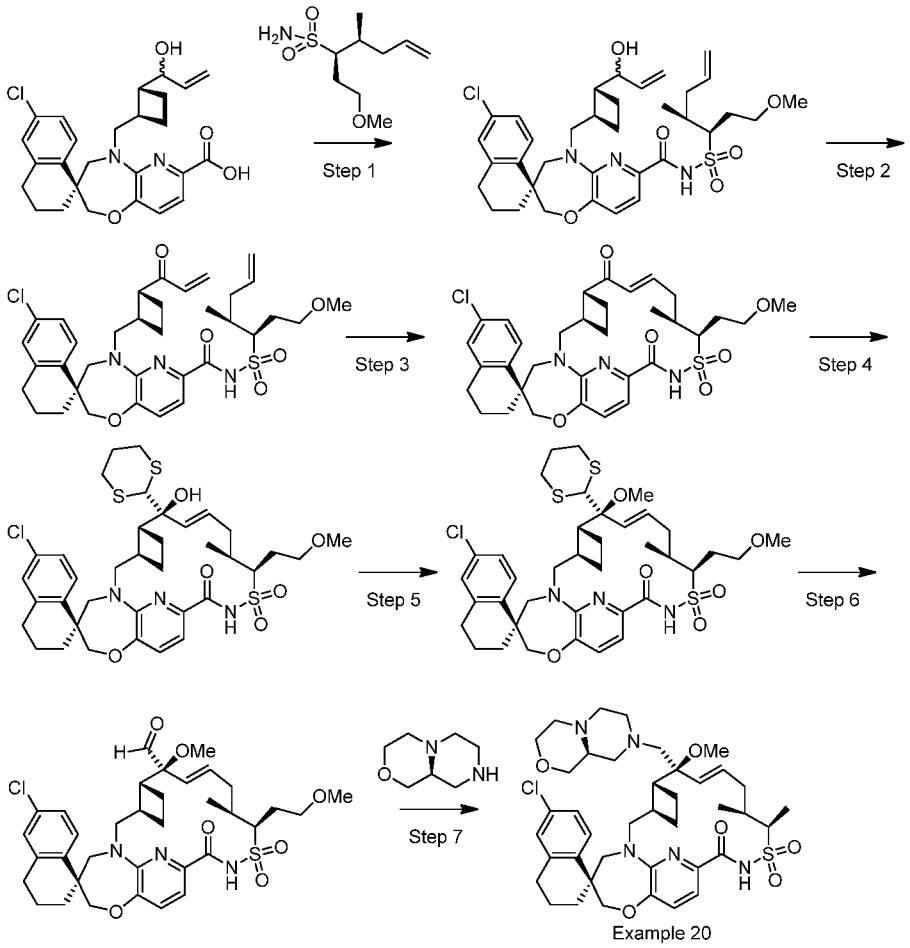
Example 19

To a solution of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide (12 mg, 0.019 mmol) and 1-(oxetan-3-yl)piperazine (26.6 mg, 0.187 mmol) in DCM (374 μL) at room temperature was added a few drop of titanium (IV) isopropoxide. The mixture was stirred at room temperature for 8 h and sodium triacetoxyborohydride (15.84 mg, 0.075 mmol) was added slowly over 1 min. The reaction was stirred for overnight and quenched with 5 mL of 1 N HCl solution. The aqueous phase was extracted with DCM (3 x). The combined organic extracts were concentrated. The residue was purified by prep-HPLC to give (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-(3-oxetanyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide as a TFA salt. MS (ESI, +ve ion) *m/z* 768.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOH-d_4) δ ppm 1.11 (d, J=6.65 Hz, 3 H), 1.39 (d, J=7.24 Hz, 3 H), 1.44 – 1.58 (m, 1 H,) 1.64 – 2.01 (m, 6 H), 2.03 – 2.27 (m, 2 H), 2.29 – 2.43 (m, 2 H,) 2.45 – 2.56 (m, 1 H), 2.32 – 3.04 (m, 7 H), 3.35 –

3.67 (m, 6 H), 3.35 – 3.65 (m, 6 H), 3.72 – 3.93 (m, 4 H), 4.03 – 4.10 (m, 1 H), 4.12 – 4.28 (m, 2 H), 4.61 (t, J=6.16 Hz, 2 H), 4.69 – 4.77 (m, 2 H), 5.78-5.90 (m, 2 H), 7.12 (d, J=1.96 Hz, 1 H), 7.15 – 7.20 (m, 1 H), 7.21-7.26 (m, 2 H), 7.70 (d, J=8.41 Hz, 1 H).

Example 20

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide



Step 1: (1S)-6-chloro-5'-(((1R,2R)-2-(1-hydroxyallyl)cyclobutyl)methyl)-N-(((3R,4S)-1-methoxy-4-methylhept-6-en-3-yl)sulfonyl)-3,4,4',5'-tetrahydro-2H,2'H-spiro[naphthalene-1,3'-pyrido[3,2-b][1,4]oxazepine]-7'-carboxamide

To a solution of (3R,4S)-1-methoxy-4-methylhept-6-ene-3-sulfonamide (4.94 g, 22.34 mmol) in DCM (80 mL) was added (1S)-6-chloro-5'-(((1R,2R)-2-(1-hydroxyallyl)cyclobutyl)methyl)-3,4,4',5'-tetrahydro-2H,2'H-spiro[naphthalene-1,3'-pyrido[3,2-b][1,4]oxazepine]-7'-carboxylic acid (6.8 g, 11.5 mmol), 4-(dimethylamino) pyridine (4.20 g, 34.4 mmol), triethylamine (3.2 mL, 23.0 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide HCl (6.6 g, 34.4 mmol). The resulting mixture was stirred at room temperature under nitrogen for 20 h. The reaction was quenched with 2 N HCl (5 mL) and diluted with water (30 mL). The aqueous layer was extracted with DCM (2 x 40 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography (330 g of silica, 0% to 40% acetone in heptane) to obtain (1S)-6-chloro-5'-(((1R,2R)-2-(1-hydroxyallyl)cyclobutyl)methyl)-N-(((3R,4S)-1-methoxy-4-methylhept-6-en-3-yl)sulfonyl)-3,4,4',5'-tetrahydro-2H,2'H-spiro[naphthalene-1,3'-pyrido[3,2-b][1,4]oxazepine]-7'-carboxamide as light brown solid (6.1 g). ^{1}H NMR (DICHLOROMETHANE-d_2) δ 10.43 (br. S., 1H), 7.70 (d, J=8.4 Hz, 1H), 7.52 (d, J=7.8 Hz, 1H), 7.19 (d, J=7.8 Hz, 2H), 7.10 (s, 1H), 5.67-5.87 (m, 2H), 5.19 (d, J=17.2 Hz, 1H), 5.01-5.12 (m, 3H), 4.60 (d, J=13.7 Hz, 1H), 4.10-4.20 (m, 1H), 3.96-4.07 (m, 3H), 3.89 (d, J=14.7 Hz, 1H), 3.53 (t, J=6.4 Hz, 1H), 3.43-3.50 (m, 1H), 3.34-3.42 (m, 1H), 3.19-3.25 (m, 2H), 3.13 (s, 1H), 2.82-2.92 (m, 1H), 2.73-2.82 (m, 2H), 2.55-2.69 (m, 1H), 2.37-2.48 (m, 1H), 2.33 (br. S., 1H), 2.04-2.22 (m, 3H), 1.91-2.01 (m, 4H), 1.76-1.91 (m, 2H), 1.62-1.74 (m, 1H), 1.54-1.61 (m, 1H), 1.41 (t, J=12.8 Hz, 1H), 1.07 (dd, J=11.2, 7.0 Hz, 3H). MS (ESI, +ve ion) *m/z* 672.4 $(M+H)^+$.

Step 2: (S)-5'-(((1R,2R)-2-acryloylcyclobutyl)methyl)-6-chloro-N-(((3R,4S)-1-methoxy-4-methylhept-6-en-3-yl)sulfonyl)-3,4,4',5'-tetrahydro-2H,2'H-spiro[naphthalene-1,3'-pyrido[3,2-b][1,4]oxazepine]-7'-carboxamide

To a solution of (1S)-6-chloro-5'-(((1R,2R)-2-(1-hydroxyallyl)cyclobutyl)methyl)-N-(((3R,4S)-1-methoxy-4-methylhept-6-en-3-yl)sulfonyl)-3,4,4',5'-tetrahydro-2H,2'H-spiro[naphthalene-1,3'-pyrido[3,2-b][1,4]oxazepine]-7'-carboxamide (6.1 g, 9.07 mmol) in DCM (70 mL) at 0 °C was added Dess-Martin periodinane (4.5 g, 10.61 mmol). After the addition, the ice bath was removed and the resulting mixture was warmed up to room temperature and stirred for 20 h. The reaction was quenched with 10% sodium thiosulfate (5 mL) and stirred for 30 min. The resulting mixture was washed with saturated $NaHCO_3$ (30 mL). The aqueous layer was extracted with DCM (2 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography (330 g of silica, 0% to 40% acetone in heptane) to obtain (S)-5'-(((1R,2R)-2-acryloylcyclobutyl)methyl)-6-chloro-N-(((3R,4S)-1-methoxy-4-methylhept-6-en-3-yl)sulfonyl)-3,4,4',5'-tetrahydro-2H,2'H-spiro[naphthalene-1,3'-pyrido[3,2-b][1,4]oxazepine]-7'-carboxamide as light brown foam. ^{1}H NMR (DICHLOROMETHANE-d_2) δ 9.25-9.54 (m, 1H), 7.70-7.76 (m, 1H), 7.44-7.51 (m, 1H), 7.14-7.21 (m, 1H), 7.03-7.13 (m, 2H), 5.85-6.03 (m, 2H), 4.13-4.22 (m, 1H), 4.01-4.12 (m, 2H), 3.85-3.99 (m, 1H), 3.72-3.81 (m, 1H), 3.58-3.70 (m, 2H), 3.29-3.33 (m, 7H), 3.17-3.27 (m, 6H), 2.94-3.04 (m, 3H), 2.83-2.93 (m, 4H), 2.73-2.80 (m, 2H), 2.51-2.64 (m, 1H), 2.32-2.41 (m, 1H), 2.23-2.31 (m, 1H), 2.05-2.12 (m, 2H), 1.97-2.05 (m, 1H), 1.87-1.96 (m, 2H), 1.76-1.87 (m, 2H), 1.61-1.70 (m, 2H), 1.51-1.59 (m, 5H), 1.40-1.51 (m, 2H), 1.04-1.11 (m, 5H), 0.96-1.02 (m, 3H). MS (ESI, +ve ion) *m/z* 670.2 $(M+H)^+$.

Step 3: (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,7'H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7',15'-dione 13',13'-dioxide

To a solution of (S)-5'-(((1R,2R)-2-acryloylcyclobutyl)methyl)-6-chloro-N-(((3R,4S)-1-methoxy-4-methylhept-6-en-3-yl)sulfonyl)-3,4,4',5'-tetrahydro-2H,2'H-spiro[naphthalene-1,3'-pyrido[3,2-b][1,4]oxazepine]-7'-carboxamide (2.2

g, 3.28 mmol) in 1,2-dichloroethane (1200 mL) under nitrogen was added Hoveyda-Grubbs catalyst 2nd generation (0.206 g, 0.328 mmol). The resulting mixture was heated at 55 °C for 20 h. The reaction was cooled to room temperature and concentrated. The crude product was purified by column chromatography (220 g of silica, 0% to 30% acetone in heptane) to obtain (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,7'H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7',15'-dione 13',13'-dioxide as pale yellow solid (1.5 g). ^{1}H NMR (DICHLOROMETHANE-d_2) δ 8.69 (s, 1H), 7.72 (d, J=8.4 Hz, 1H), 7.20 (d, J=8.4 Hz, 1H), 7.08-7.18 (m, 3H), 6.71-6.82 (m, 1H), 5.86-5.96 (m, 1H), 4.44 (dd, J=14.1, 8.4 Hz, 1H), 4.14 (d, J=12.1 Hz, 1H), 3.99 (d, J=12.1 Hz, 1H), 3.92 (d, J=15.3 Hz, 1H), 3.85-3.89 (m, 1H), 3.73-3.82 (m, 1H), 3.70 (dd, J=8.0, 5.1 Hz, 1H), 3.59-3.66 (m, 1H), 3.42 (s, 3H), 3.39 (d, J=14.7 Hz, 1H), 2.94 (dd, J=14.0, 3.8 Hz, 1H), 2.82-2.90 (m, 1H), 2.72-2.82 (m, 2H), 2.35-2.45 (m, 1H), 2.26-2.34 (m, 1H), 2.09-2.19 (m, 3H), 1.97-2.06 (m, 2H), 1.75-1.94 (m, 5H), 1.37-1.48 (m, 1H), 1.18 (d, J=6.8 Hz, 3H). MS (ESI, +ve ion) *m/z* 642.2 $(M+H)^+$.

Step 4: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-hydroxy-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

An oven dry 50 mL 3-neck flask, which was equipped with stir bar and temperature probe, was added 1,3-dithiane (0.890 g, 7.40 mmol) and THF (15 mL). The resulting mixture was cooled between -20 to -30 °C and n-butyllithium solution (2.5 M in hexanes, 2.7 mL, 6.75 mmol) was added dropwise via syringe. The resulting mixture was stirred at -20 °C for 30 min, cooled below -70 °C and stirred for 20 min. To this reaction was added lanthanum(III) chloride lithium chloride complex (0.6 M in THF, 5.6 mL, 3.36 mmol, Strem Chemical, Newbury Port, MA) dropwise via syringe (internal temperature was kept below -70 °C).

After 10 min, (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,7'H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7',15'-dione 13',13'-dioxide (0.430 g, 0.670 mmol) in THF (5 mL) was added dropwise via syringe (internal temperature was kept below -70 °C). The reaction was stirred at -70 °C for 15 min after the addition. The reaction was quenched with saturated NH_4Cl (3 mL), warmed to room temperature and partitioned between EtOAc (60 mL) and water (30 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography (80 g of silica, 0% to 30% acetone in heptane) gave (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-hydroxy-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide as white solid (0.350 g). ^{1}H NMR (DICHLOROMETHANE-d_2) δ 9.24 (br. S., 1H), 7.65-7.73 (m, 1H), 7.35-7.41 (m, 1H), 7.19 (d, J=7.8 Hz, 2H), 7.11 (s, 1H), 5.76-5.87 (m, 1H), 5.60-5.71 (m, 1H), 4.61 (dd, J=13.5, 4.9 Hz, 1H), 4.12-4.22 (m, 2H), 3.94-4.03 (m, 2H), 3.89 (d, J=14.5 Hz, 1H), 3.53-3.63 (m, 2H), 3.44 (d, J=14.5 Hz, 1H), 3.32 (s, 3H), 2.94-3.04 (m, 2H), 2.85-2.93 (m, 4H), 2.73-2.84 (m, 3H), 2.54-2.70 (m, 2H), 2.17-2.33 (m, 2H), 2.04-2.13 (m, 4H), 1.87-2.00 (m, 3H), 1.71-1.83 (m, 3H), 1.64 (dt, J=18.6, 9.5 Hz, 1H), 1.47 (d, J=14.9 Hz, 1H), 1.15 (d, J=6.8 Hz, 3H). MS (ESI, +ve ion) *m/z* 762.2 $(M+H)^+$.

Step 5: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

To a 15 mL flask was added (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-hydroxy-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-

[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16, 18,24]tetraen]-15'-one 13',13'-dioxide (0.350 g, 0.459 mmol) and THF (15.0 mL). The mixture was cooled to 0 °C and sodium hydride (60 weight percent in oil, 0.165 g, 4.13 mmol) was added. The ice bath was removed after the addition and the mixture was stirred at room temperature for 20 min then iodomethane (0.520 mL, 8.37 mmol) was added. The mixture was stirred at room temperature for 2 h then quenched with water (5 mL). The resulting mixture was partitioned between EtOAc (50 mL) and water (20 ml). The organic layers was dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography (40 g of silica, 0% to 30% acetone in heptane) gave (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16, 18,24]tetraen]-15'-one 13',13'-dioxide as white solid. ^{1}H NMR (DICHLOROMETHANE-d_2) δ 9.20 (br. S., 1H), 7.69 (d, J=8.4 Hz, 1H), 7.36 (d, J=7.8 Hz, 1H), 7.16-7.22 (m, 2H), 7.11 (s, 1H), 5.73-5.86 (m, 1H), 5.49-5.60 (m, 1H), 4.82 (dd, J=14.0, 5.0 Hz, 1H), 4.37 (s, 1H), 4.09-4.20 (m, 2H), 3.99 (d, J=12.3 Hz, 1H), 3.91 (d, J=14.5 Hz, 1H), 3.56-3.71 (m, 2H), 3.40-3.50 (m, 1H), 3.33 (s, 3H), 3.22 (s, 3H), 3.09 (br. S., 1H), 2.92-3.00 (m, 1H), 2.83-2.91 (m, 4H), 2.75-2.83 (m, 2H), 2.66-2.74 (m, 1H), 2.63 (br. S., 1H), 2.17-2.33 (m, 2H), 2.04-2.14 (m, 3H), 1.91 (td, J=11.7, 3.6 Hz, 4H), 1.71-1.80 (m, 1H), 1.62-1.70 (m, 2H), 1.54-1.62 (m, 1H), 1.39-1.49 (m, 1H), 1.15 (d, J=6.8 Hz, 3H). MS (ESI, +ve ion) *m/z* 776.2 $(M+H)^+$.

Step 6: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16, 18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide

To a solution of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo

[14.7.2.0~3,6~.0~19,24~] pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (0.250 g, 0.322 mmol) in acetonitrile (12.0 mL) was added calcium carbonate (0.161 g, 1.610 mmol), water (3.00 mL), and iodomethane (0.250 mL, 4.02 mmol). The resulting mixture was heated at 40 °C for 20 h. The reaction was partitioned between water (20 mL) and DCM (50 mL). The aqueous layer was extracted with DCM (30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The purification by column chromatography (24 g of silica, 0% to 30% acetone in heptane) gave (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide as white solid (0.130 g). ^{1}H NMR (DICHLOROMETHANE-d_2) δ 9.74 (s, 1H), 9.50 (s, 1H), 7.72 (d, J=8.4 Hz, 1H), 7.47 (d, J=7.8 Hz, 1H), 7.21 (d, J=8.0 Hz, 2H), 7.12 (d, J=2.2 Hz, 1H), 5.69 (d, J=16.2 Hz, 1H), 5.38-5.47 (m, 1H), 4.42 (dd, J=14.0, 8.5 Hz, 1H), 4.19 (d, J=12.3 Hz, 1H), 4.04 (d, J=12.1 Hz, 1H), 3.87 (d, J=14.7 Hz, 1H), 3.60 (td, J=8.7, 4.9 Hz, 1H), 3.46-3.54 (m, 2H), 3.38-3.45 (m, 1H), 3.31 (s, 3H), 3.06 (s, 3H), 2.96 (dd, J=14.1, 5.9 Hz, 1H), 2.74-2.90 (m, 4H), 2.46 (ddd, J=11.2, 7.1, 3.7 Hz, 1H), 2.21-2.28 (m, 1H), 2.11-2.20 (m, 1H), 1.97-2.08 (m, 2H), 1.81-1.96 (m, 5H), 1.67-1.79 (m, 1H), 1.55-1.66 (m, 1H), 1.40-1.50 (m, 1H), 1.14 (d, J=6.8 Hz, 3H). MS (ESI, +ve ion) *m/z* 686.2 $(M+H)^+$.

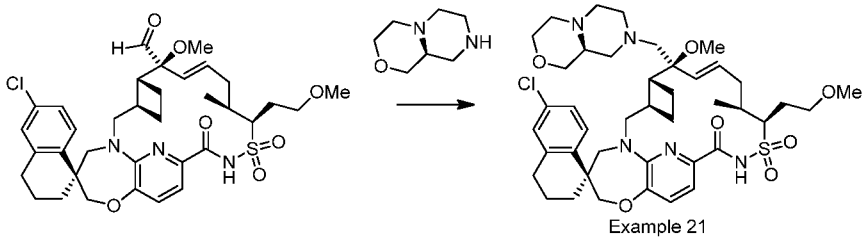
Step 7: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

To a solution of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,

18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide (0.080 g, 0.117 mmol) in DCM (4.0 mL) was added (S)-octahydropyrazino[2,1-c][1,4]oxazine (0.093 g, 0.653 mmol) in DCM (4.0 mL) and acetic acid (1 drop). The mixture was stirred at room temperature under nitrogen for 1 h. Sodium triacetoxyborohydride (0.100 g, 0.472 mmol) was added and the mixture was stirred at room temperature for 1 h. The reaction was partitioned between water (10 mL) and DCM (20 mL). The aqueous layer was extracted with DCM (20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography (24 g of silica, 0% to 10% MeOH in DCM) gave (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide as white solid (0.066 g). ^{1}H NMR (DICHLOROMETHANE-d_2) δ 7.70 (d, J=8.4 Hz, 1H), 7.40 (d, J=7.8 Hz, 1H), 7.19 (d, J=8.4 Hz, 1H), 7.08-7.16 (m, 2H), 5.53-5.66 (m, 2H), 4.13-4.19 (m, 1H), 4.02-4.12 (m, 2H), 3.74-3.83 (m, 2H), 3.65-3.73 (m, 1H), 3.53-3.63 (m, 3H), 3.46 (d, J=14.7 Hz, 1H), 3.32 (s, 4H), 2.98-3.10 (m, 7H), 2.74-2.85 (m, 2H), 2.72 (d, J=6.1 Hz, 1H), 2.52-2.64 (m, 3H), 2.46 (d, J=16.8 Hz, 3H), 2.23-2.37 (m, 2H), 2.06-2.15 (m, 1H), 1.96-2.03 (m, 2H), 1.85-1.94 (m, 4H), 1.72-1.81 (m, 2H), 1.45-1.63 (m, 6H), 1.08 (d, J=6.8 Hz, 3H). One exchangeable proton was not observed. MS (ESI, +ve ion) *m/z* 812.4 $(M+H)^+$.

Example 21

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

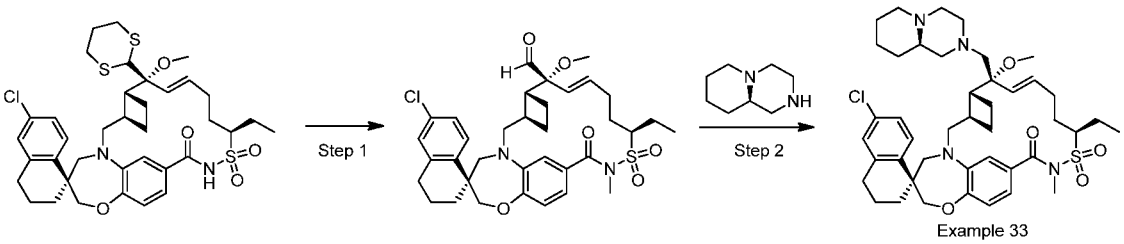


Example 21

To a solution of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide (0.140 g, 0.204 mmol) in DCM (5.0 mL) was added (R)-octahydro-1H-pyrido[1,2-a]pyrazine (0.160 g, 1.141 mmol) in DCM (1 mL) and AcOH (2 drops). The mixture was stirred at room temperature under nitrogen for 1 h then treated with sodium triacetoxyborohydride (0.173 g, 0.816 mmol). The resulting mixture was stirred for 1 h then partitioned between water (10 mL) and DCM (20 mL). The aqueous layer was extracted with DCM (20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography (24 g of silica, 0% to 10% MeOH in DCM) gave (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide as white solid (0.120 g). ^{1}H NMR (DICHLOROMETHANE-d_2) δ 7.69-7.76 (m, 1H), 7.42-7.50 (m, 1H), 7.18 (dd, J=8.5, 2.1 Hz, 1H), 7.04-7.14 (m, 2H), 5.77 (br. S., 2H), 4.17 (d, J=12.9 Hz, 1H), 4.00-4.13 (m, 2H), 3.77 (d, J=14.5 Hz, 1H), 3.64-3.73 (m, 1H), 3.57 (d, J=9.2 Hz, 2H), 3.35-3.47 (m, 1H), 3.21-3.34 (m, 5H), 3.09 (br. S., 3H), 2.99 (br. S., 1H), 2.83-2.95 (m, 2H), 2.65-2.82 (m, 5H), 2.55 (br. S., 2H), 2.25-2.44 (m, 3H), 2.09-2.21 (m, 1H), 1.97-2.08 (m, 3H), 1.89 (d, J=19.2 Hz, 4H), 1.61-1.73 (m, 4H), 1.38-1.51 (m, 4H), 1.29-1.35 (m, 1H), 1.17 (br. S., 2H), 1.02 (d, J=6.8 Hz, 4H). One exchangeable proton was not observed. MS (ESI, +ve ion) *m/z* 810.4 $(M+H)^+$.

Example 33

(1S,3'R,6'R,7'R,8'E,12'R)-6-chloro-12'-ethyl-7'-methoxy-14'-methyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide



Step 1: (1S,3'R,6'R,7'R,8'E,12'R)-6-chloro-12'-ethyl-7'-methoxy-14'-methyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide

A 2-dram vial was charged with (1S,3'R,6'R,7'R,8'E,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-12'-ethyl-7'-methoxy-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (27 mg, 0.037 mmol; Accessed via General Methods 1 (R^1 = H, using (S)-6'-chloro-5-(((1R,2R)-2-((S)-1-hydroxyallyl)cyclobutyl)methyl)-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylic acid and (R)-hept-6-ene-3-sulfonamide) and General Methods 5 (using MeI)), a magnetic stir bar, acetonitrile (820 μL) and water (205 μL). To the resulting suspension was added calcium carbonate (18.5 mg, 0.185 mmol) and iodomethane (23 μL, 0.37 mmol). The vial was sealed and the mixture stirred at 45 °C. Additional iodomethane (10 equiv) was added after 2.5 h, 19 h, 23 h, and 27 h. After a 51 h reaction time, the reaction was quenched by adding saturated aqueous ammonium chloride (1 mL)

and water (1 mL). The mixture was extracted with EtOAc (3 × 2 mL) and the combined organic extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford a mixture of (1S,3'R,6'R,7'R,8'E,12'R)-6-chloro-12'-ethyl-7'-methoxy-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide and (1S,3'R,6'R,7'R,8'E,12'R)-6-chloro-12'-ethyl-7'-methoxy-14'-methyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide in a 3:1 ratio that was carried forward in the next step without purification.

Step 2: (1S,3'R,6'R,7'R,8'E,12'R)-6-chloro-12'-ethyl-7'-methoxy-14'-methyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

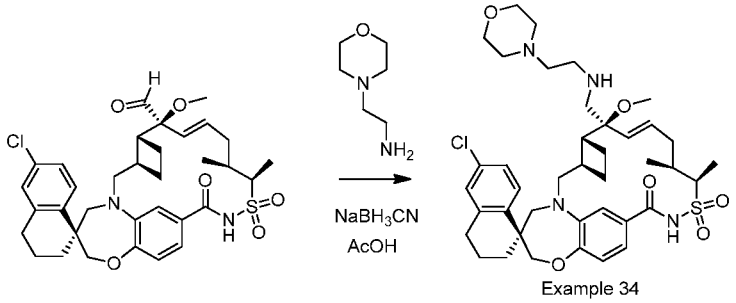
A 1 mL vial was charged with a 3:1 mixture of (1S,3'R,6'R,7'R,8'E,12'R)-6-chloro-12'-ethyl-7'-methoxy-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide and (1S,3'R,6'R,7'R,8'E,12'R)-6-chloro-12'-ethyl-7'-methoxy-14'-methyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide (0.022 g, 0.034 mmol), (R)-octahydro-1H-pyrido[1,2-a]pyrazine (26.5 mg, 0.189 mmol; Aurum Pharmatech, Franklin Park, NJ), a magnetic stir bar, and 1,2-dichloroethane (343 µL). The resulting mixture was stirred for 1 h before the addition of sodium triacetoxyborohydride (3.6 mg, 0.017 mmol). After 45 min, a second portion of

sodium triacetoxyborohydride (3.6 mg, 0.017 mmol) was added and the reaction was continued for an additional 2 h before a third portion of sodium triacetoxyborohydride (3.6 mg, 0.017 mmol) was added. After an additional 3 h, the reaction was quenched by adding methanol. (1S,3'R,6'R,7'R,8'E,12'R)-6-chloro-12'-ethyl-7'-methoxy-14'-methyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide was isolated as the corresponding TFA salt after purification via RP-HPLC (Column: Phenomenex Luna, C18, 150 x 21 mm; Solvent: A = water (0.1% TFA), B = (R) (0.1% TFA), 30 mL/min, 30% B to 100% B over 18 min then 2 min at 100% B): 5.2 mg (0.006 mmol, 17% yield); MS (ESI, +ve ion) *m/z* 779.3 $(M+H)^+$.

Example 34

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((2-(4-morpholinyl)ethyl)amino)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

General Method 13



Example 34

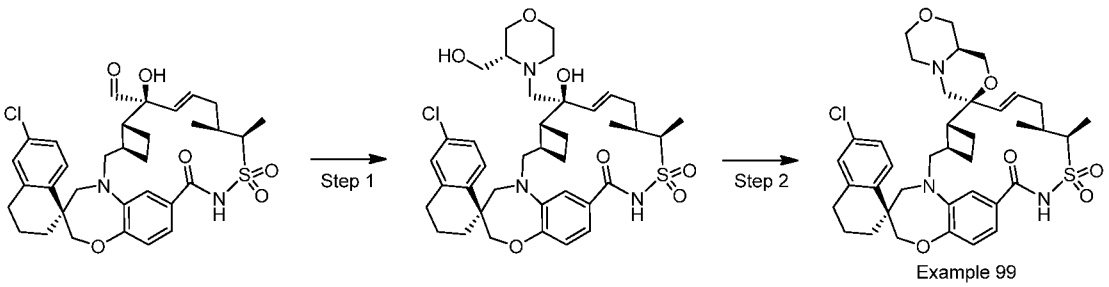
A solution of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-15'-oxo-7'-methoxy-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,2

4]tetraene]-7'-carbaldehyde 13',13'-dioxide (52 mg, 0.081 mmol) and 2-morpholinoethanamine (106 μL, 0.811 mmol) in THF (810 μL) was stirred at ambient temperature for 90 min. Sodium cyanotrihydroborate (25.5 mg, 0.405 mmol) and acetic acid (93 μL, 1.6 mmol) were added and the reaction mixture was stirred at ambient temperature for 1 h. The reaction mixture was diluted with EtOAc (2 mL) and washed with saturated aqueous sodium bicarbonate (5 mL); the layers were partitioned and the aqueous layer was washed with EtOAc (2 x 5 mL). The organic extracts were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford an off-white solid.

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((2-(4-morpholinyl)ethyl)amino)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide was isolated as the corresponding TFA salt after purification via RP-HPLC (Column: Phenomenex Luna, C18, 150 x 21 mm; Solvent: A = water (0.1% TFA), B = (R) (0.1% TFA), 30 mL/min, 30% B to 100% B over 18 min then 2 min at 100% B): 41.8 mg (0.048 mmol, 59% yield); MS (ESI, +ve ion) *m/z* 755.2 $(M+H)^+$.

Example 99

(1S,3'R,6'R,7'S,8'E,9a''S,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4,6'',7'',9'',9a''-hexahydro-1''H,2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-7',3''-[1,4]oxazino[3,4-c][1,4]oxazin]-15'-one 13',13'-dioxide



Step 1: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(((3R)-3-(hydroxymethyl)-4-morpholinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

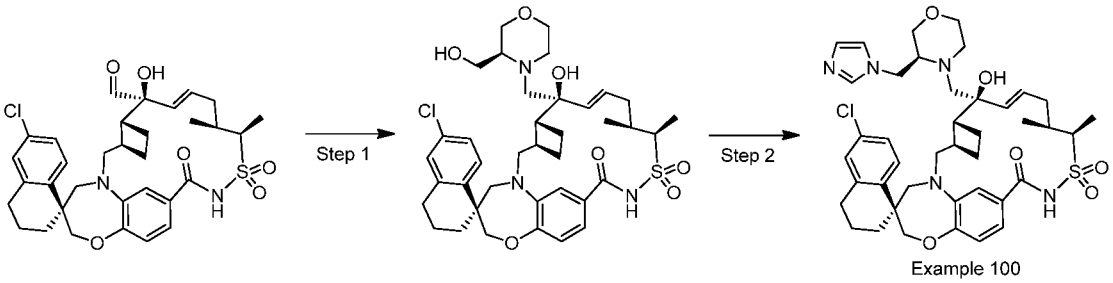
To a room temperature mixture of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide (0.050 g, 0.080 mmol) and (R)-morpholin-3-ylmethanol hydrochloride (0.124 g, 0.807 mmol; J&W Pharmlab, Levittown, PA) was added N,N-diisopropylethylamine (0.230 mL, 1.32 mmol) via syringe. After 30 min, 1.0 M sodium cyanoborohydride in tetrahydrofuran (0.400 mL, 0.400 mmol) and acetic acid (0.100 mL, 1.73 mmol) were added and the reaction was allowed to stir at room temperature overnight. The reaction mixture was quenched with satd NH_4Cl and the aqueous layer was extracted with DCM (3x). The combined organic layers were evaporated onto silica gel and purified by flash chromatography (Isco, (4 gram HP)) eluting with 0% to 100% 2 M NH_3 in MeOH in DCM to give 70 mg of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(((3R)-3-(hydroxymethyl)-4-morpholinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide as a white crystalline solid. (ESI, +ve ion) *m/z* 728.3 $(M+1)^+$.

Step 2: (1S,3'R,6'R,7'S,8'E,9a''S,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4,6'',7'',9'',9a''-hexahydro-1''H,2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-7',3''-[1,4]oxazino[3,4-c][1,4]oxazin]-15'-one 13',13'-dioxide

To a room temperature solution of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(((3R)-3-(hydroxymethyl)-4-morpholinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide in tetrahydrofuran (0.3 mL) was added 60% sodium hydride in mineral oil (0.011 g, 0.275 mmol) as a solid. After 30 min the mixture was cooled (0 °C) and treated with 1-(p-toluenesulfonyl)imidazole (0.064 g, 0.288 mmol) and the reaction was allowed to warm to room temperature overnight. The reaction mixture was quenched with saturated NH_4Cl and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were evaporated onto silica gel and purified by flash chromatography (Isco, (4 gram HP)) eluting with 2 M NH_3 in MeOH:CH_2Cl_2 (0:1 → 1:9) to afford (1S,3'R,6'R,7'S,8'E,9a''S,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4,6'',7'',9'',9a''-hexahydro-1''H,2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-7',3''-[1,4]oxazino[3,4-c][1,4]oxazin]-15'-one 13',13'-dioxide (2.1 mg, 9%) as a tan crystalline solid. MS (ESI, +ve ion) *m/z* 710.3 $(M+1)^+$.

Example 100

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(((3S)-3-(1H-imidazol-1-ylmethyl)-4-morpholinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide



Example 100

Step 1: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(((3S)-3-(hydroxymethyl)-4-morpholinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

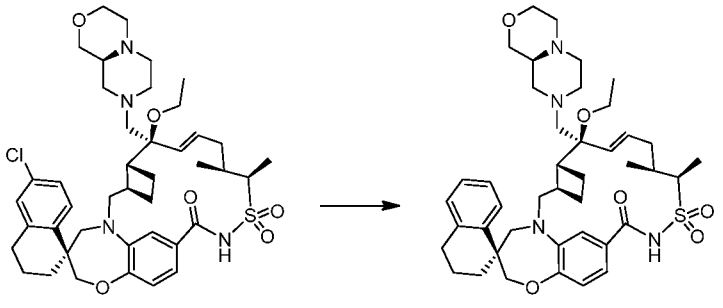
To a room temperature mixture of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide (0.052 g, 0.083 mmol) and 3(S)-hydroxymethylmorpholine (0.099 g, 0.845 mmol; J&W Pharmlab, Levittown, PA) in tetrahydrofuran (2 mL) was added N,N-diisopropylethylamine (0.250 mL, 1.437 mmol). After 1 h, 1.0 M sodium cyanoborohydride in tetrahydrofuran (0.450 mL, 0.450 mmol) and acetic acid (0.100 mL, 1.73 mmol) were added and the reaction was stirred overnight. The reaction mixture was quenched with pH 7 buffer and the aqueous layer was extracted with DCM (3x). The combined organic layers were evaporated onto silica gel and purified by flash chromatography (Isco (4 g)) eluting with 25% EtOH/EtOAc:heptane (0:1 → 1:1) to give (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(((3S)-3-(hydroxymethyl)-4-morpholinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (46 mg, 76%) as a white crystalline solid. (ESI, +ve ion) *m/z* 728.2 $(M+1)^+$.

Step 2: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(((3S)-3-(1H-imidazol-1-ylmethyl)-4-morpholinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

To a room temperature solution of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(((3S)-3-(hydroxymethyl)-4-morpholinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide in tetrahydrofuran (1 mL) was added sodium hydride (0.020 g, 0.51 mmol) as a solid. After 30 min the reaction was cooled (0 °C) and treated with 1-(p-toluenesulfonyl)imidazole (0.112 g, 0.505 mmol). After stirring overnight the reaction mixture was quenched with pH 7 buffer and the aqueous layer was extracted with DCM (3x). The combined organic layers were evaporated onto silica gel and purified by flash chromatography (Isco (4 g)) eluting with 25% EtOH/EtOAc:heptane (0:1 → 1:0) to give (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(((3S)-3-(1H-imidazol-1-ylmethyl)-4-morpholinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (27 mg, 55%) as a white crystalline solid. (ESI, +ve ion) *m/z* 778.3 $(M+1)^+$.

Example 105

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-7'-ethoxy-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

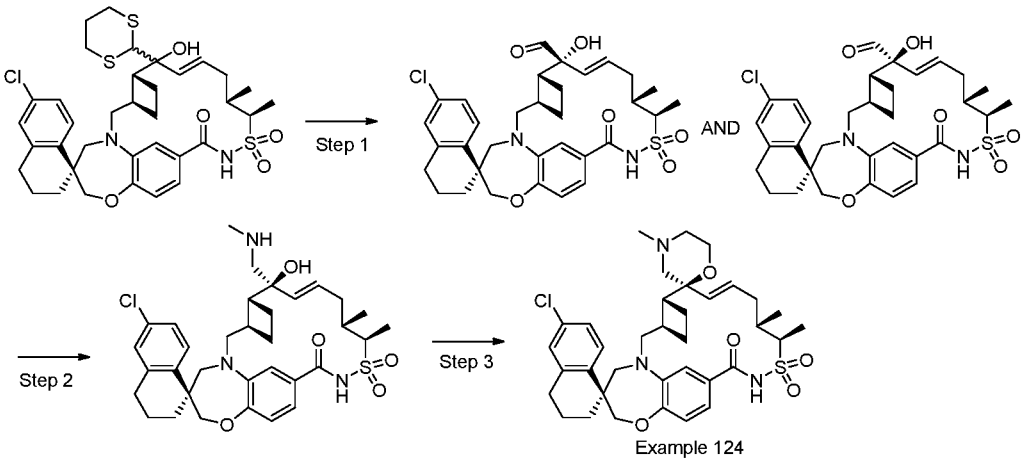


Example 101 Example 105

A mixture of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-ethoxy-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (0.010 g, 0.013 mmol) and palladium, 10 wt.% (dry basis) on activated carbon, wet, degussa type (0.005 g, 2.3 μmol) in EtOAc (1 mL) was stirred at room temperature under hydrogen (18 psig) overnight. The reaction was filtered through a pad of Celite and the pad was washed with EtOAc. The filtrate was concentrated under reduced pressure, diluted with MeOH and purified by reverse-phase HPLC (Gilson; Gemini-NX C18 AXIA, 100 x 50 mm column) eluting with 0.1%TFA-H_2O:0.1%TFA CH_3CN (9:1 → 1:9). The fractions containing the desired product were combined and partitioned between pH 7 buffer (1 M K_2HPO_4/KH_2PO_4)/EtOAc. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to give (1S,3'R,6'R,7'S,8'E,11'S,12'R)-7'-ethoxy-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (6.5 mg, 68%) as a white crystalline solid. (ESI, +ve ion) m/z: 747.3 $(M+1)^+$.

Example 124

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-4'',11',12'-trimethyl-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-7',2''-[1,4]oxazinan]-15'-one 13',13'-dioxide



Step 1: (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide and (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide

Calcium carbonate (2.60 g, 18.5 mmol) and iodomethane (1 M in TBME; 18.5 mL, 37.1 mmol) were sequentially added to a solution of (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide and (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (2.66 g, 3.71 mmol) in acetonitrile (44 mL)/water (6.5 mL) at 50 °C; the reaction mixture was stirred at 50 °C for 16 h. The slurry was filtered to remove any excess calcium carbonate, and the filtrate was concentrated. The solid was diluted with EtOAc (150 mL); the milky mixture

was poured off; the remaining solid was diluted with DCM/IPA (3:2, 200 mL), and the combined organics were partitioned with sat. aq. NH_4Cl (100 mL). The organic layer was separated, solublized with MeOH, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was adsorbed onto silica gel and was purified via automated flash chromatography (silica gel, 0% to 50% EtOAc/heptane w/0.3% AcOH) to give (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide (396 mg, 0.631 mmol, 17% yield) and (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide (0.810, 1.29 mmol, 35% yield), both as white solids. MS (ESI, +ve) *m/z* 627.2 $(M+1)^+$ for both.

Step 2: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((methylamino)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

A mixture of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide (48 mg, 0.077 mmol), methanamine hydrochloride (91 mg, 1.3 mmol), and DIPEA (227 µL, 1.30 mmol) in DCM (383 µL)/MeOH (580 µL) was stirred at room temperature for 15 min; sodium cyanotrihydroborate (14 mg, 0.23 mmol) was then added. The slurry was stirred at room temperature for 30 min. The reaction mixture was diluted with DCM (50 mL), added to a separatory funnel, and washed with water (50 mL); the organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was adsorbed onto silica gel and was purified via automated

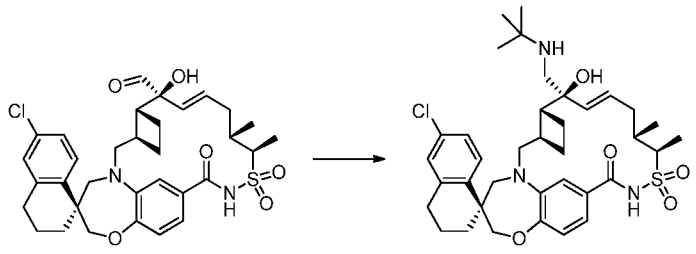
flash chromatography (silica gel, 0% to 20% MeOH/DCM) to give (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((methylamino)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (14 mg, 0.022 mmol, 29% yield) as a white film. MS (ESI, +ve) *m/z* 642.2 $(M+1)^+$.

Step 3: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-4'',11',12'-trimethyl-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-7',2''-[1,4]oxazinan]-15'-one 13',13'-dioxide

Cesium carbonate (85 mg, 0.26 mmol) was added to a solution of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((methylamino)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (14 mg, 0.022 mmol) and 1,2-dibromoethane (8 μL, 0.09 mmol) in DMF (0.22 mL) at ambient temperature. The reaction mixture was stirred at 70 °C for 16 h. 1-Tosyl-1H-imidazole (4.8 mg, 0.022 mmol) and sodium hydride (60% in mineral oil; 0.5 mg, 0.02 mmol) were added to the reaction mixture which was then stirred at ambient temperature for 20 min. The reaction mixture was diluted with EtOAc (50 mL), added to a separatory funnel, and washed with saturated, aqueous sodium bicarbonate (2 × 50 mL); the organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was adsorbed onto silica gel and was purified via automated flash chromatography (silica gel, 0% to 10% MeOH/DCM) to give (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-4'',11',12'-trimethyl-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-7',2''-[1,4]oxazinan]-15'-one 13',13'-dioxide (2 mg, 3 μmol, 14% yield) as a light yellow oil. MS (ESI, +ve) *m/z* 668.3 $(M+1)^+$.

Example 125

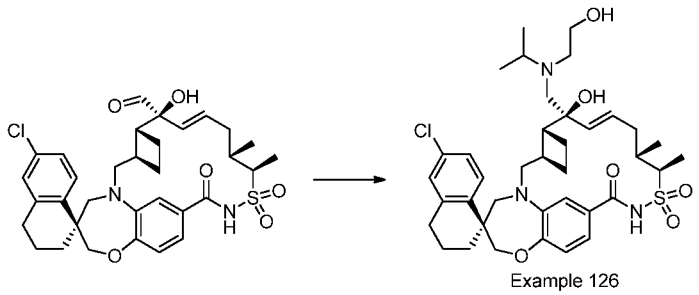
(1S,3'R,6'R,7'S,8'E,11'S,12'R)-7'-((tert-butylamino)methyl)-6-chloro-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide



A solution of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide (99 mg, 0.16 mmol) and 2-methylpropan-2-amine (115 mg, 1.58 mmol) in THF (1.6 mL) was stirred at ambient temperature for 1.5 h; sodium cyanotrihydroborate (50 mg, 0.79 mmol) and acetic acid (181 μL, 3.16 mmol) were added, and the reaction mixture was stirred at ambient temperature for 1 h. The reaction mixture was diluted with EtOAc (75 mL), added to a separatory funnel, and washed with saturated, aqueous sodium bicarbonate (100 mL); the organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was adsorbed onto silica gel and was purified via automated flash chromatography (silica gel, 0% to 10% MeOH/DCM) to give (1S,3'R,6'R,7'S,8'E,11'S,12'R)-7'-((tert-butylamino)methyl)-6-chloro-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (53 mg, 0.077 mmol, 49% yield) as a white solid. MS (ESI, +ve) *m/z* 684.3 $(M+1)^+$.

Example 126

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(((2-hydroxyethyl)(1-methylethyl)amino)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide



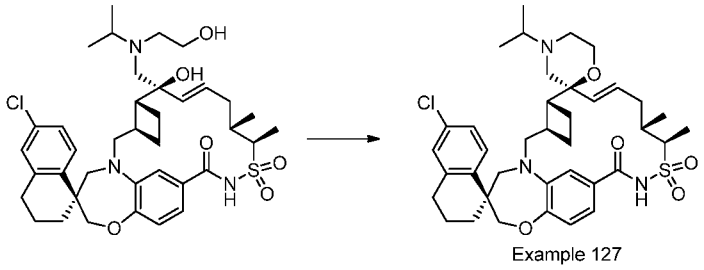
Example 126

A solution of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide (68 mg, 0.11 mmol) and 2-(isopropylamino)ethanol (Enamine, Monmouth Jct, NJ; 112 mg, 1.08 mmol) in THF (1.1 mL) was stirred at ambient temperature for 2.5 h; sodium cyanotrihydroborate (34 mg, 0.54 mmol) and acetic acid (0.1 mL, 2.2 mmol) were added, and the reaction mixture was stirred at ambient temperature for 1 h. The reaction mixture was diluted with EtOAc (75 mL), added to a separatory funnel, and washed with saturated, aqueous sodium bicarbonate (100 mL); the organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was adsorbed onto silica gel and was purified via automated flash chromatography (silica gel, 0% to 8% MeOH/DCM) to give (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(((2-hydroxyethyl)(1-methylethyl)amino)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,2

4]tetraen]-15'-one 13',13'-dioxide (20 mg, 0.028 mmol, 26% yield) as a white solid. MS (ESI, +ve) *m/z* 714.2 $(M+1)^+$.

Example 127

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-4''-(1-methylethyl)-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-7',2''-[1,4]oxazinan]-15'-one 13',13'-dioxide



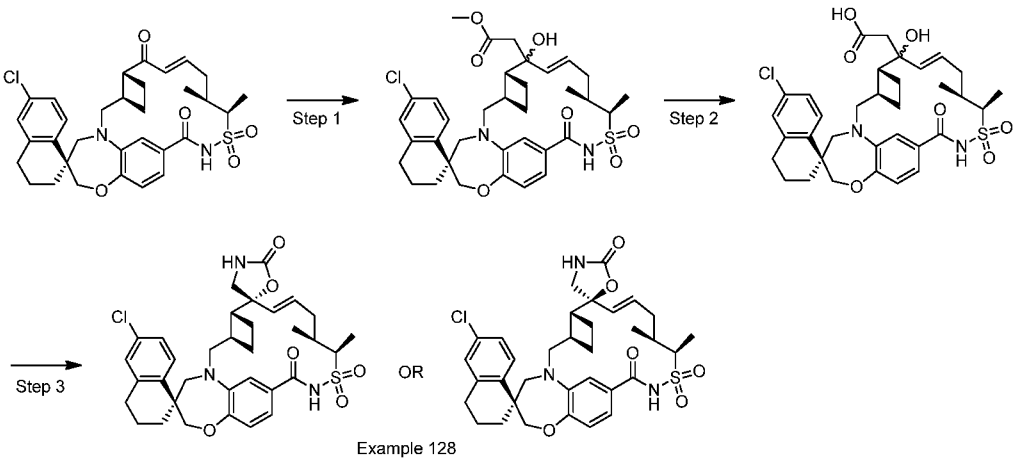
Example 127

Sodium hydride (60% in mineral oil; 3 mg, 0.07 mmol) was added to a solution of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(((2-hydroxyethyl)(1-methylethyl)amino)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (17 mg, 0.024 mmol) and 1-tosyl-1H-imidazole (6.9 mg, 0.031 mmol) in THF (0.24 mL) at 0 °C; the reaction mixture was stirred at 0 °C for 15 min. The reaction mixture was diluted with EtOAc (75 mL), added to a separatory funnel, and washed with saturated, aqueous ammonium chloride (100 mL); the organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated in vacuo. A solution of the crude product in DCM was loaded onto the column and was purified via automated flash chromatography (silica gel, 0% to 6% MeOH/DCM) to give (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-4''-(1-methylethyl)-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,2

4]tetraene-7',2''-[1,4]oxazinan]-15'-one 13',13'-dioxide (6 mg, 9 μmol, 36% yield) as a white solid. MS (ESI, +ve) *m/z*: 696.3 $(M+1)^+$.

Example 128

(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,2''H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-7',5''-[1,3]oxazolidine]-2'',15'-dione 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,2''H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-7',5''-[1,3]oxazolidine]-2'',15'-dione 13',13'-dioxide



Example 128

Step 1: methyl ((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetate and methyl ((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetate

A solution of methyl acetate (0.172 mL, 2.17 mmol) in THF (1 mL) was added dropwise to a stirred solution of lithium diisopropylamide (1.0 M solution in hexanes/tetrahydrofuran, 2.17 mL, 2.17 mmol) in THF (1 mL) at -78 °C. The mixture was stirred at -78 °C for 0.5 h before a solution of (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,7'H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7',15'-dione 13',13'-dioxide (216 mg, 0.362 mmol) in THF (2 mL) was added slowly via syringe. The reaction mixture was stirred at -78 °C for 1.5 h before being allowed to warm to room temperature and quenched with water (15 mL). The mixture was extracted with EtOAc (25 mL). The organic layer was separated, washed with 1 M aqueous HCl (15 mL), washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give a crude mixture of methyl ((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetate and methyl ((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetate (246 mg, 0.366 mmol, 101 % yield) as a yellow solid that was used directly in the next step. MS (ESI, +ve ion) *m/z* 671.3 $(M+H)^+$.

Step 2: ((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetic acid and ((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetic acid

Lithium hydroxide (2.0 M aqueous, 0.453 mL, 0.905 mmol) was added to a stirred solution of methyl ((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetate and methyl ((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetate (243 mg, 0.362 mmol) in tetrahydrofuran (7 mL). The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL) and extracted three times with EtOAc (50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatographic purification of the residue (silica gel, 0% to 100% EtOAc with 0.3% AcOH as a modifier in heptane) gave the desired product contaminated with AcOH. The isolated product was azeotroped with toluene to give a mixture of ((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetic acid and ((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetic acid (66 mg, 0.100 mmol, 27.7 % yield) as a white solid. MS (ESI, +ve ion) *m/z* 657.2 $(M+H)^+$.

Step 3: (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,2''H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-7',5''-[1,3]oxazolidine]-2'',15'-dione 13',13'-dioxide or

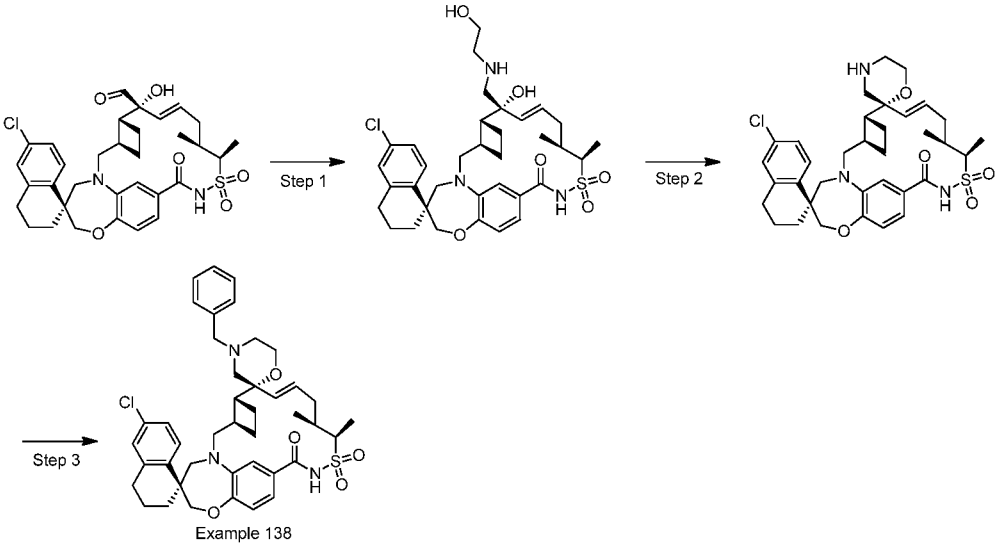
(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,2''H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-7',5''-[1,3]oxazolidine]-2'',15'-dione 13',13'-dioxide

A mixture of ((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetic acid and ((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetic acid (66 mg, 0.100 mmol), triethylamine (0.031 mL, 0.221 mmol), and diphenylphosphoryl azide (0.024 mL, 0.110 mmol) in tert-butanol (2 mL) was refluxed for 2.5 h. The reaction mixture was concentrated in vacuo. Chromatographic purification of the residue (silica gel, 0% to 100% EtOAc with 0.3% AcOH as a modifier in heptane) provided (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,2''H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-7',5''-[1,3]oxazolidine]-2'',15'-dione 13',13'-dioxide or (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,2''H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-7',5''-[1,3]oxazolidine]-2'',15'-dione 13',13'-dioxide (30 mg, 0.046 mmol, 45.7 % yield) as a white solid. MS (ESI, +ve ion) *m/z* 654.2 $(M+H)^+$.

Example 138

(1S,3'R,6'R,7'R,8'E,11'S,12'R)-4''-benzyl-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-

[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-7',2''-[1,4]oxazinan]-15'-one 13',13'-dioxide



Example 138

Step 1: (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(((2-hydroxyethyl)amino)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

A mixture of (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide (199 mg, 0.317 mmol) and 2-aminoethanol (322 mg, 5.27 mmol) was stirred in dichloromethane (6 mL) for 20 min before acetic acid (0.366 mL, 6.35 mmol) and sodium cyanoborohydride (59.8 mg, 0.952 mmol) were added. The reaction mixture was stirred at room temperature for 17 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (40 mL) and extracted with EtOAc (50 mL). The organic layer was separated, washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatographic purification of the residue (silica gel, 0% to 10% 2 M ammonia in MeOH in DCM) provided

(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(((2-hydroxyethyl)amino)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (115 mg, 0.171 mmol, 53.9 % yield) as a white solid. MS (ESI, +ve ion) *m/z* 672.2 $(M+H)^+$.

Step 2: (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-7',2''-[1,4]oxazinan]-15'-one 13',13'-dioxide

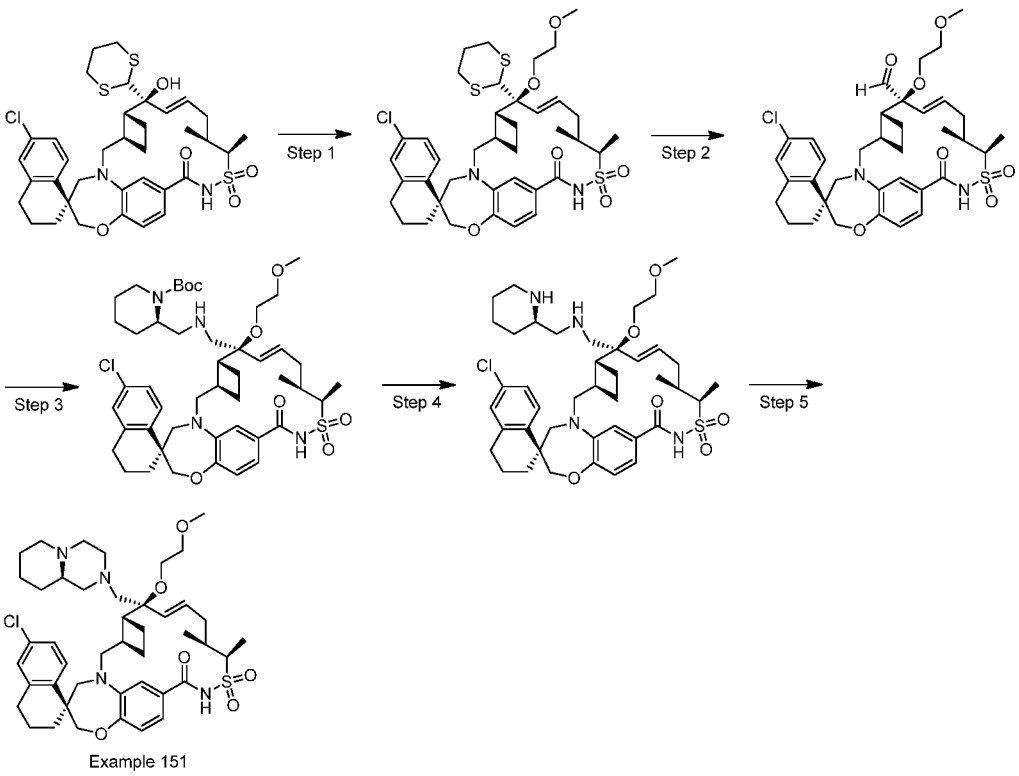
Sodium hydride (60% dispersion in mineral oil, 20.5 mg, 0.513 mmol) was added to a stirred suspension of (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(((2-hydroxyethyl)amino)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (115 mg, 0.171 mmol) in tetrahydrofuran (5 mL) at room temperature. The mixture was stirred for 20 min before being cooled to 0 °C, followed by addition of 1-(p-toluenesulfonyl)imidazole (38.0 mg, 0.171 mmol). The reaction mixture was stirred at 0 °C for 5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (30 mL). The organic layer was separated, washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatographic purification of the residue (silica gel, 0% to 10% 2 M ammonia in MeOH in DCM) provided (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-7',2''-[1,4]oxazinan]-15'-one 13',13'-dioxide (67 mg, 0.102 mmol, 60% yield) as a white solid. MS (ESI, +ve ion) *m/z* 654.2 $(M+H)^+$.

Step 3: (1S,3'R,6'R,7'R,8'E,11'S,12'R)-4''-benzyl-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-7',2''-[1,4]oxazinan]-15'-one 13',13'-dioxide

(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-Chloro-11',12'-dimethyl-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-7',2''-[1,4]oxazinan]-15'-one 13',13'-dioxide (17 mg, 0.026 mmol), (bromomethyl)benzene (3.40 µl, 0.029 mmol), and triethylamine (7.95 µl, 0.057 mmol) were mixed in acetonitrile (0.25 mL). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (15 mL). The organic layer was separated, washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatographic purification of the residue (silica gel, 0 to 10% 2 M ammonia in MeOH in DCM) provided (1S,3'R,6'R,7'R,8'E,11'S,12'R)-4''-benzyl-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-7',2''-[1,4]oxazinan]-15'-one 13',13'-dioxide (9 mg, 0.012 mmol, 47% yield) as a white solid. MS (ESI, +ve ion) *m/z* 744.3 $(M+H)^+$.

Example 151

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-methoxyethoxy)-11',12'-dimethyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide



Example 151

Step 1: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-(2-methoxyethoxy)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

To a solution of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (460 mg, 0.641 mmol) in tetrahydrofuran (8 mL) was added sodium hydride, 60% dispersion in mineral oil (679 mg, 19.24 mmol) in portions. After addition, the mixture was then stirred at room temperature under nitrogen for 10 min, then 2-bromoethyl methyl ether (1.809 mL, 19.24 mmol) was added. The resulting mixture was stirred at room temperature for 14 h. The mixture was quenched with saturated NH_4Cl (150 mL)and was extracted with EtOAc (2 x 200 mL). The combined organic extracts

were dried over $MgSO_4$ and concentrated in vacuo. Chromatographic purification of the residue (silica gel, 0% to 100% EtOAc/heptane) provided (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-(2-methoxyethoxy)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (391 mg, 0.504 mmol, 79 % yield) as a light yellow solid. MS (ESI, +ve ion) *m/z* 699.2, 755.3 $(M+H)^+$.

Step 2: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-methoxyethoxy)-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide

A solution of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-(2-methoxyethoxy)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (391 mg, 0.504 mmol) in acetonitrile (10 mL) and water (2.500 mL) was added methyl iodide (0.313 mL, 5.04 mmol) and calcium carbonate (252 mg, 2.52 mmol). The resulting mixture was then stirred at 50 °C for 14 h. The mixture was quenched with saturated NH_4Cl and was extracted with EtOAc (2 x 100 mL). The combined organic extracts were then dried over $MgSO_4$ and concentrated in vacuo. Chromatographic purification of the residue (silica gel, 0% to 100% EtOAc/heptane) provided (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-methoxyethoxy)-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide (233 mg, 0.340 mmol, 67.4 % yield) as a light yellow solid. MS (ESI, +ve ion) *m/z* 685.3 $(M+H)^+$.

Step 3: 2-methyl-2-propanyl (2R)-2-(((((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-methoxyethoxy)-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-

dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)methyl)amino)methyl)-1-piperidinecarboxylate

A solution of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-methoxyethoxy)-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide (55 mg, 0.080 mmol) and (R)-tert-butyl 2-(aminomethyl)piperidine-1-carboxylate (172 mg, 0.803 mmol) in 1,2-dichloroethane (0.8 mL) was stirred at room temperature for 14 h. Sodium triacetoxyborohydride (0.059 mL, 0.401 mmol) was added to the mixture and the mixture was then stirred at room temperature for 1 h. The mixture was diluted with MeOH (5 mL) and silica gel was added. The mixture was concentrated and dried in vacuo. The solid mixture was then purified by silica gel column chromatography (solid loading, 0% to 100% EtOAc/heptane) provided 2-methyl-2-propanyl (2R)-2-(((((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-methoxyethoxy)-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)methyl)amino)methyl)-1-piperidinecarboxylate (64 mg, 0.072 mmol, 90 % yield) as a light yellow solid. MS (ESI, +ve ion) *m/z* 883.5 $(M+H)^+$.

Step 4: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-methoxyethoxy)-11',12'-dimethyl-7'-((((2R)-2-piperidinylmethyl)amino)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

To a solution of 2-methyl-2-propanyl (2R)-2-(((((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-methoxyethoxy)-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-

[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)methyl)amino)methyl)-1-piperidinecarboxylate (58 mg, 0.066 mmol) in dichloromethane (0.5 mL) was added trifluoroacetic acid (0.098 mL, 1.3 mmol). The resulting mixture was then stirred at room temperature for 2 h. The mixture was cooled to 0°C and *i*Pr$_2$Net (0.457 mL, 2.63 mmol) was added followed by 1,2-dibromoethane (0.023 mL, 0.263 mmol) and DMA (0.1 mL). The resulting mixture was then stirred at room temperature for 72 h and at 50 °C for 1 h. The mixture was concentrated in vacuo and chromatographic purification of the residue (silica gel, 0% to 100% EtOAc/heptane) provided (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-methoxyethoxy)-11',12'-dimethyl-7'-((((2R)-2-piperidinylmethyl)amino)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide as a colorless oil, which was used in the next step. MS (ESI, +ve ion) *m/z* 783.3 $(M+H)^+$.

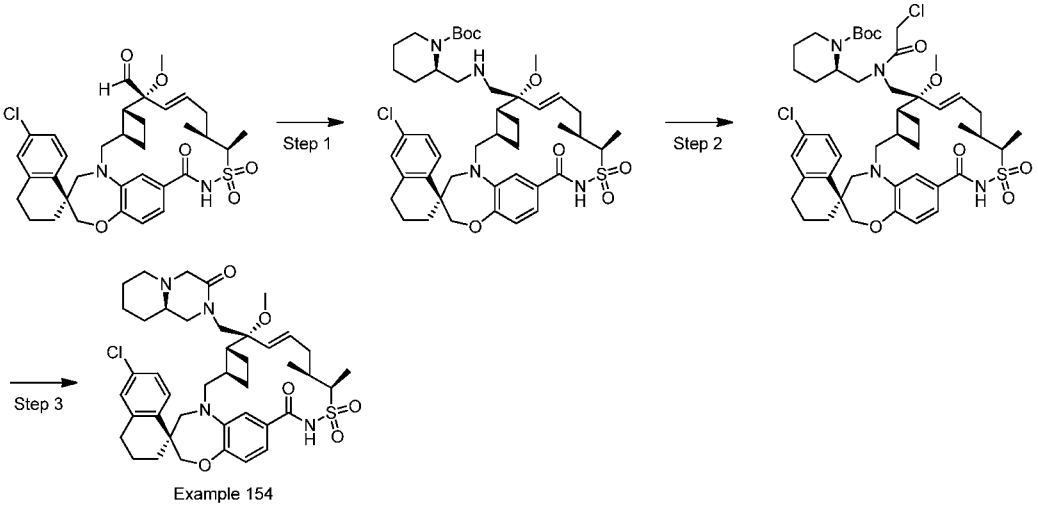
Step 5: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-methoxyethoxy)-11',12'-dimethyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

To a solution of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-methoxyethoxy)-11',12'-dimethyl-7'-((((2R)-2-piperidinylmethyl)amino)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (51.4 mg, 0.066 mmol) in N, N-dimethylacetamide (0.4 mL) was added *i*Pr$_2$Net (0.057 mL, 0.328 mmol) and 1,2-dibromoethane (0.028 mL, 0.328 mmol). The resulting mixture was then stirred at room temperature for 14 h. Then, 1,2-dibromoethane (0.2 mL) was added and the mixture was stirred at room temperature for 14 h then at 55 °C for 72 h. The mixture was purified by silica gel column chromatography (0% to 10%

MeOH/DCM) provided (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-methoxyethoxy)-11',12'-dimethyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (17 mg, 0.021 mmol, 32.0 % yield) as a light yellow solid. MS (ESI, +ve ion) *m/z* 809.2 $(M+H)^+$.

Example 154

(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aR)-3-oxooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide



Step 1: 2-methyl-2-propanyl (2R)-2-(((((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)methyl)amino)methyl)-1-piperidinecarboxylate

To a solution of (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide (44 mg, 0.069 mmol) in 1,2-dichloroethane (1 mL) was added (R)-tert-butyl 2-(aminomethyl)piperidine-1-carboxylate (147 mg, 0.686 mmol). The resulting mixture was then stirred at room temperature for 1 h. Then, sodium triacetoxyborohydride (73 mg, 0.343 mmol) was added in portions. After addition, the mixture was then stirred at room temperature for 3 d. The mixture was purified by silica gel column chromatography (0% to 20% MeOH/DCM) to provide 2-methyl-2-propanyl (2R)-2-(((((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)methyl)amino)methyl)-1-piperidinecarboxylate (57.6 mg, 0.069 mmol, 100 % yield) as a light yellow solid, which was used in the next step. MS (ESI, +ve ion) *m/z* 839.4 $(M+H)^+$.

Step 2: 2-methyl-2-propanyl (2R)-2-(((chloroacetyl)(((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)methyl)amino)methyl)-1-piperidinecarboxylate

To a solution of 2-methyl-2-propanyl (2R)-2-(((((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)methyl)amino)methyl)-1-piperidinecarboxylate (57.6 mg, 0.069 mmol) in dichloromethane (1.5 mL) at -78 °C under nitrogen was added chloroacetyl chloride (10.92 µL, 0.137 mmol) followed by *i*Pr$_2$Net (0.036 mL, 0.206 mmol). After addition, the mixture was then stirred at -78 °C for 1.5 h. Chloroacetyl chloride (0.022 mL) was added and the mixture was stirred at -25 °C

for 1 h and placed in a -20 °C freezer for 16 h. The mixture was quenched with MeOH (2 mL) and concentrated in vacuo. Chromatographic purification (silica gel, 0% to 100% EtOAc/heptane) provided 2-methyl-2-propanyl (2R)-2-(((chloroacetyl)(((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)methyl)amino)methyl)-1-piperidinecarboxylate (62.8 mg, 0.069 mmol, 100 % yield) as a light yellow solid. MS (ESI, +ve ion) *m/z* 937.3, 939.2 $(M+Na)^+$.

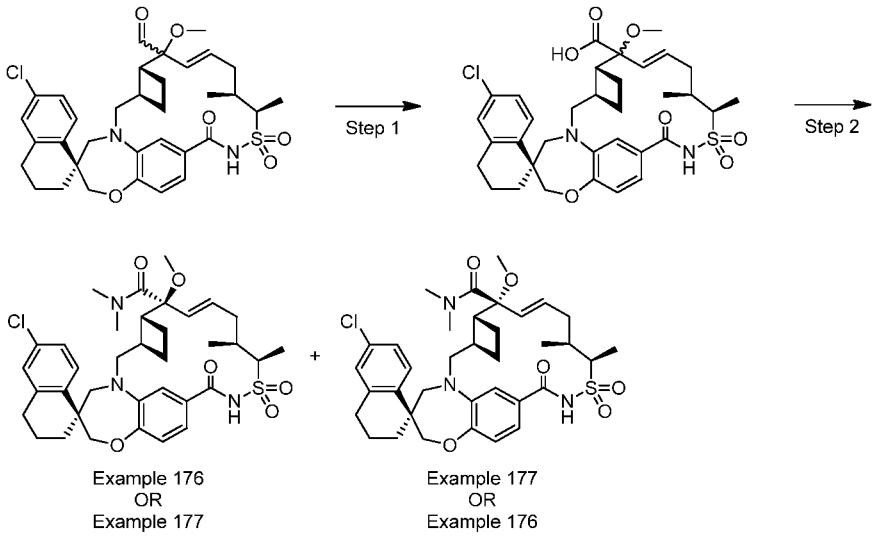
Step 3: (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aR)-3-oxooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

To a solution of 2-methyl-2-propanyl (2R)-2-(((chloroacetyl)(((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)methyl)amino)methyl)-1-piperidinecarboxylate (61.8 mg, 0.067 mmol) in dichloromethane (1 mL) was added trifluoroacetic acid (0.251 mL, 3.37 mmol). After addition, the mixture was then stirred at room temperature for 17 min. The mixture was cooled to -78 °C and *i*PrNEt (0.704 mL, 4.05 mmol) was added dropwise. After addition, the mixture was stirred at room temperature for 14 h. The mixture was purified by silica gel column chromatography (0% to 20% MeOH/DCM) followed by preparative HPLC (Phenomenex Gemini C18 column, 150×30 mm, 10% to 100% 0.1% TFA in MeCN/H_2O) provided a desired product in a solution of MeCN/H_2O 0.1% TFA. The pH was adjusted to 7 with buffer (KH_2PO_4/K_2HPO_4) and extracted with EtOAc (2 x 10 mL). The combined extracts were washed with brine, dried (Na_2SO_4), concentrated, and dried in vacuo to provide (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-

dimethyl-7'-(((9aR)-3-oxooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (33 mg, 0.042 mmol, 62.8 % yield) as an off white solid. MS (ESI, +ve ion) *m/z* 779.3 $(M+H)^+$.

Examples 176 and 177

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-N,N,11',12'-tetramethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carboxamide 13',13'-dioxide AND
(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-N,N,11',12'-tetramethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carboxamide 13',13'-dioxide



Step 1: (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-15'-oxo-7'-methyoxy-3,4-dihydro-2H-spiro[naphthalene-1,22'-

[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carboxylic acid 13',13'-dioxide

To a 15-mL round-bottomed flask was added (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-15'-oxo-7'-methoxy-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide (18 mg, 0.028 mmol, a mixture of two epimers) and 2-methyl-2-butene (149 μL, 1.404 mmol) in tert-butanol (281 μL) and water (281 μL). Potassium phosphate monobasic (38.2 mg, 0.281 mmol) and sodium chlorite (25.4 mg, 0.281 mmol) was added to the solution. The solution was stirred at room temperature for 1 h. The reaction mixture was diluted with saturated Na_2SO_3 (5 mL) and extracted with DCM (3 x10 mL). The organic extract was washed with saturated NaCl (10 mL) and dried over $MgSO_4$. The solution was filtered and concentrated in vacuo to give an off-white solid. The material was used in the next step without further purification. MS (ESI, +ve ion) *m/z* 657.2 $(M+H)^+$.

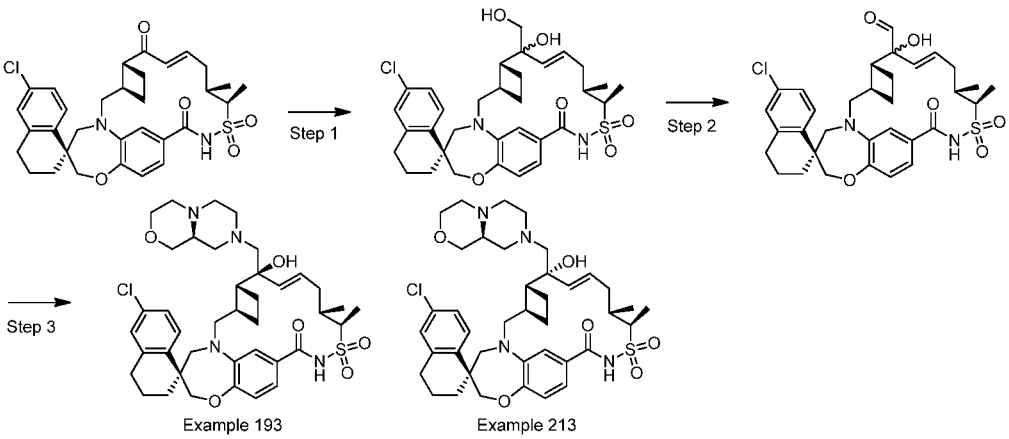
Step 2: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-N,N,11',12'-tetramethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carboxamide 13',13'-dioxide AND (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-N,N,11',12'-tetramethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carboxamide 13',13'-dioxide

To a 5-mL round-bottomed flask was added (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-15'-oxo-7'-methyoxy-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carboxylic acid 13',13'-dioxide (13 mg, 0.020 mmol, a mixture of

two epimers) and diethylamine (2 M in THF, 39.6 µL, 0.079 mmol) in DCM (396 µL). 1-Propanephosphonic acid cyclic anhydride (50 wt. % solution in ethyl acetate, 62.9 µL, 0.099 mmol) was added at room temperature. The solution was stirred at room temperature for 2 h. The reaction mixture was diluted with saturated $NaHCO_3$ (5 mL) and extracted with EtOAc (2 x 10 mL). The organic layer was concentrated. The crude material was further purified by prep-HPLC to give two products. The first peak collected was assigned to be Example 176 and the second peak was assigned to be Example 177. MS (ESI, +ve ion) *m/z* 684.2 $(M+H)^+$ for both isomers.

Examples 193 and 213

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide and (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide



Step 1: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-CHLORO-7'-HYDROXY-7'-(HYDROXYMETHYL)-11',12'-DIMETHYL-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[8,16,18,24]TETRAEN]-15'-ONE 13',13'-DIOXIDE AND (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-CHLORO-7'-HYDROXY-7'-(HYDROXYMETHYL)-11',12'-DIMETHYL-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[8,16,18,24]TETRAEN]-15'-ONE 13',13'-DIOXIDE

To a stirred ice-cooled solution of (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,7'H,15'H-spiro[naphthalene-1,22'[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7',15'-dione 13',13'-dioxide (1.015 g, 1.700 mmol) and trimethylsulfonium iodide (0.364 g, 1.785 mmol) in dimethyl sulfoxide (4.0 mL) was dropwise added potassium tert-butoxide, 1.0 M solution in tetrahydrofuran (4.25 mL, 4.25 mmol) under argon. The resulting mixture was stirred in the ice bath for 5 min and at ambient temperature for 30 min. The crude reaction mixture was directly loaded onto a silica gel precolumn (25 g) previously covered with a layer of ammonium chloride and subjected to combi-flash column chromatography on a 24 g ISCO gold column eluting with 0% to 100% EtOAc/Hexanes followed by 5% to 20 % MeOH/DCM to give an approximately 3:1 mixture of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(hydroxymethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide and (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(hydroxymethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (0.82 g, 1.3 mmol, 79% yield) as a white solid. MS (ESI, +ve ion) *m/z* 629.2 $(M+1)^+$.

Step 2: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-CHLORO-7'-HYDROXY-11',12'-DIMETHYL-15'-OXO-3,4-DIHYDRO-2H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[8,16,18,24]TETRAENE]-7'-CARBALDEHYDE 13',13'-DIOXIDE AND (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-CHLORO-7'-HYDROXY-11',12'-DIMETHYL-15'-OXO-3,4-DIHYDRO-2H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[8,16,18,24]TETRAENE]-7'-CARBALDEHYDE 13',13'-DIOXIDE

To a stirred ice-cooled solution of a mixture of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(hydroxymethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide and (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(hydroxymethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (180 mg, 0.286 mmol) in DCM (5.0 mL) was added under argon Dess-Martin periodinane (121 mg, 0.286 mmol) in one portion as a solid. The resulting mixture was stirred under argon at 0 °C for 10 min and at ambient temperature for a period of 3 h. The crude mixture was directly loaded onto a silica gel precolumn (25 g) and subjected to combi-flash column chromatography on a 12 g ISCO gold column eluting with 0% to 20 % MeOH/DCM to give 180 mg of an impure mixture of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide and (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,2

4]tetraene]-7'-carbaldehyde 13',13'-dioxide as an off-white solid. It was taken onto the next step without further purification. MS (ESI, +ve ion) *m/z* 627.2 $(M+1)^+$.

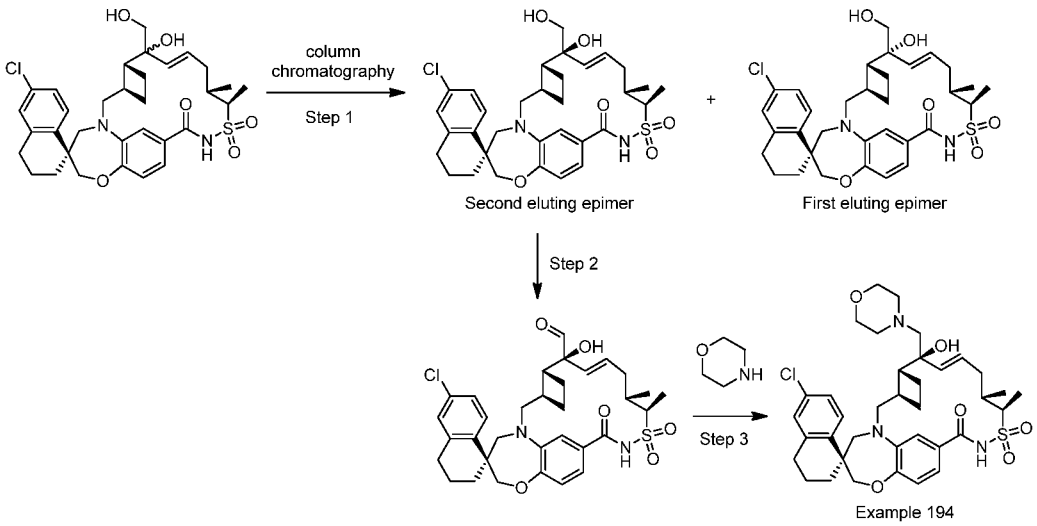
Step 3: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-CHLORO-7'-((9AS)-HEXAHYDROPYRAZINO[2,1-C][1,4]OXAZIN-8(1H)-YLMETHYL)-7'-HYDROXY-11',12'-DIMETHYL-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[8,16,18,24]TETRAEN]-15'-ONE 13',13'-DIOXIDE AND (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-CHLORO-7'-((9AS)-HEXAHYDROPYRAZINO[2,1-C][1,4]OXAZIN-8(1H)-YLMETHYL)-7'-HYDROXY-11',12'-DIMETHYL-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[8,16,18,24]TETRAEN]-15'-ONE 13',13'-DIOXIDE

The title compounds were prepared from a mixture of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide and (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide according to General Method 10. (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (Example 193) was the second eluting epimer off the silica gel column. MS (ESI, +ve ion) *m/z* 753.3 $(M+1)^+$.

(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (Example 213) was the first eluting epimer off the silica gel column. MS (ESI, +ve ion) *m/z* 753.3 $(M+1)^+$.

Example 194

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-CHLORO-7'-HYDROXY-11',12'-DIMETHYL-7'-(4-MORPHOLINYLMETHYL)-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[8,16,18,24]TETRAEN]-15'-ONE 13',13'-DIOXIDE



Step 1: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-CHLORO-7'-HYDROXY-7'-(HYDROXYMETHYL)-11',12'-DIMETHYL-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[8,16,18,24]TETRAEN]-15'-ONE 13',13'-DIOXIDE

The title compound was obtained as a single stereoisomer from a silica gel column chromatography separation of an epimeric mixture of

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(hydroxymethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide and (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(hydroxymethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide eluting with 1% to 20 % MeOH/DCM. The title compound was the second eluting epimer off the silica gel column. MS (ESI, +ve ion) *m/z* 629.3 $(M+1)^+$.

Step 2: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-CHLORO-7'-HYDROXY-11',12'-DIMETHYL-15'-OXO-3,4-DIHYDRO-2H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[8,16,18,24]TETRAENE]-7'-CARBALDEHYDE 13',13'-DIOXIDE

The title compound was synthesized from (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(hydroxymethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide according to the protocol in Example 193 (Step 2). MS (ESI, +ve ion) *m/z* 627.4 $(M+1)^+$.

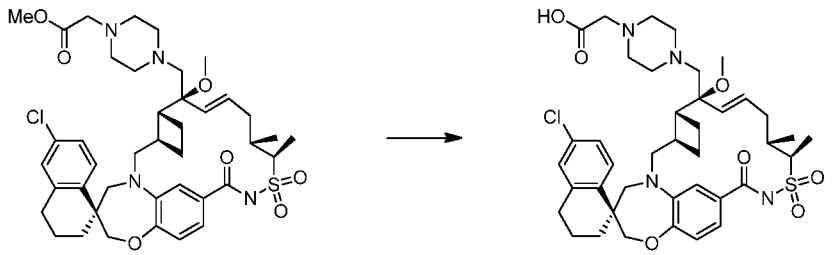
Step 3: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-CHLORO-7'-HYDROXY-11',12'-DIMETHYL-7'-(4-MORPHOLINYLMETHYL)-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[8,16,18,24]TETRAEN]-15'-ONE 13',13'-DIOXIDE

The title compound was synthesized from (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-

[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide according to General Method 10. MS (ESI, +ve ion) *m/z* 698.5 $(M+1)^+$.

Example 270

(4-(((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-CHLORO-7'-METHOXY-11',12'-DIMETHYL-13',13'-DIOXIDO-15'-OXO-3,4-DIHYDRO-2H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[8,16,18,24]TETRAEN]-7'-YL)METHYL)-1-PIPERAZINYL)ACETIC ACID



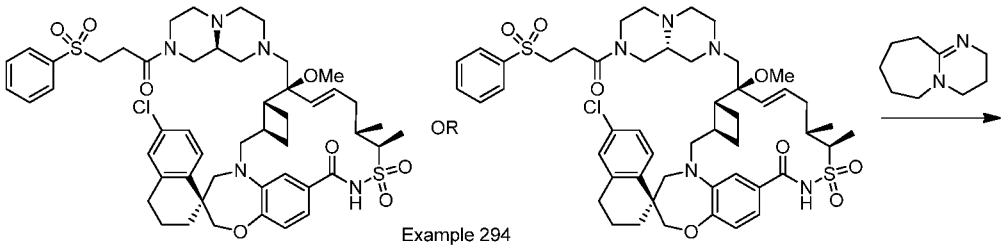
Example 269 Example 270

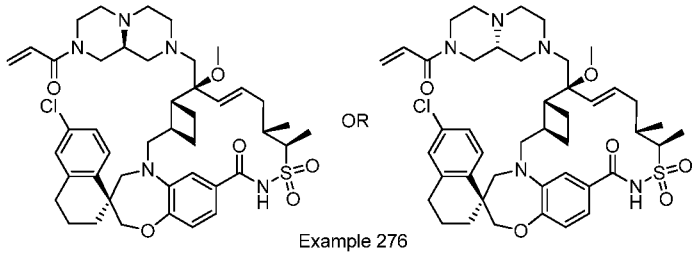
To a stirred solution of methyl (4-(((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)methyl)-1-piperazinyl)acetate (Example 269) (15 mg, 0.019 mmol) in MeOH (1.5 mL) and water (0.5 mL) was added lithium hydroxide hydrate (8.0 mg, 0.19 mmol). The resulting mixture was stirred at room temperature for 3 h. The residue was taken up in MeOH and subjected to preparative reverse-phase HPLC (Gemini™ Prep C18 10 µm column; Phenomenex, Torrance, CA; gradient elution of 20 to 90% MeCN in water, where both solvents contain 0.1% TFA, a 15-min gradient in a 24-min method) to give, after lyophilization, 11 mg of (4-(((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-

[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)methyl)-1-piperazinyl)acetic acid as a white solid. MS (ESI, +ve ion) *m/z* 769.7 $(M+1)^+$.

Example 276

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-7'-(((9AS)-8-ACRYLOYLOCTAHYDRO-2H-PYRAZINO[1,2-A]PYRAZIN-2-YL)METHYL)-6-CHLORO-7'-METHOXY-11',12'-DIMETHYL-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[8,16,18,24]TETRAEN]-15'-ONE 13',13'-DIOXIDE OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-7'-(((9AR)-8-ACRYLOYLOCTAHYDRO-2H-PYRAZINO[1,2-A]PYRAZIN-2-YL)METHYL)-6-CHLORO-7'-METHOXY-11',12'-DIMETHYL-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[8,16,18,24]TETRAEN]-15'-ONE 13',13'-DIOXIDE





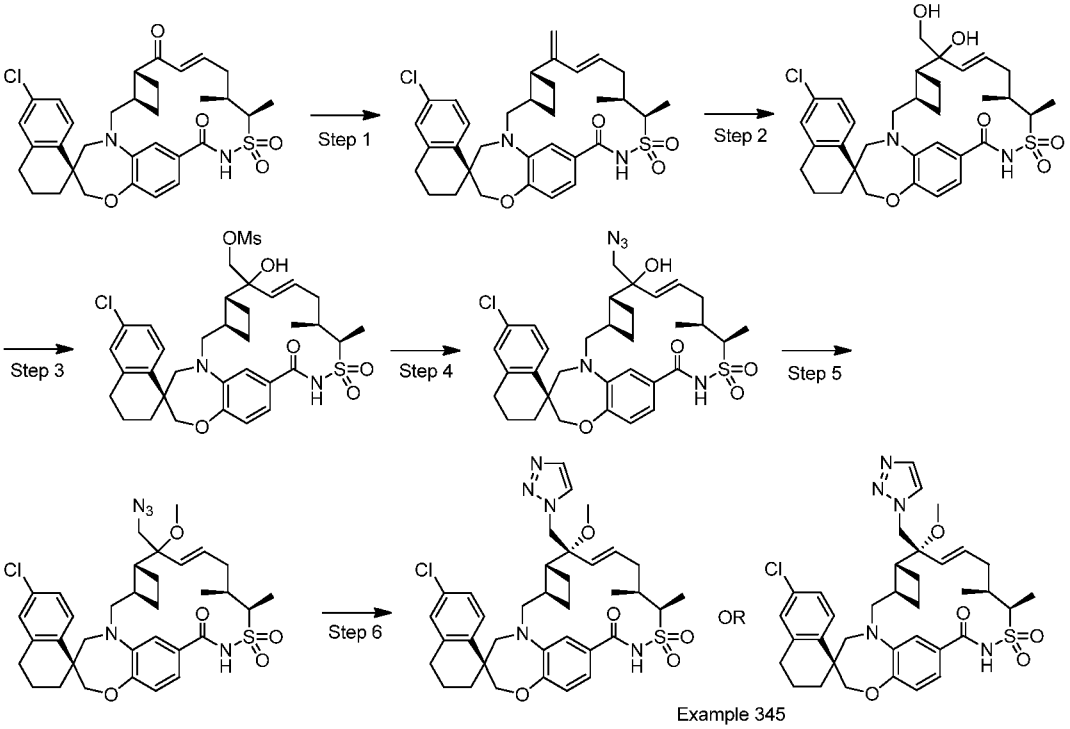
A solution of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aS)-8-(3-(phenylsulfonyl)propanoyl)octahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-

[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aR)-8-(3-(phenylsulfonyl)propanoyl)octahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (15 mg, 0.016 mmol) and 1,8-diazabicyclo-[5.4.0]undec-7-ene (0.15 mL, 1.0 mmol) in pyridine (0.30 mL) in a microwave reaction vessel was subjected to microwave irradiation for 50 min at 75 °C. The crude mixture was taken up in MeOH and subjected to preparative reverse-phase HPLC (Gemini™ Prep C_{18} 10 μm column; Phenomenex, Torrance, CA; gradient elution of 20 to 90% MeCN in water, where both solvents contain 0.1% TFA, a 15-min gradient in a 24-min method) to give, after lyophilization, 7.5 mg of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-7'-(((9AS)-8-ACRYLOYLOCTAHYDRO-2H-PYRAZINO[1,2-A]PYRAZIN-2-YL)METHYL)-6-CHLORO-7'-METHOXY-11',12'-DIMETHYL-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[8,16,18,24]TETRAEN]-15'-ONE 13',13'-DIOXIDE OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-7'-(((9AR)-8-ACRYLOYLOCTAHYDRO-2H-PYRAZINO[1,2-A]PYRAZIN-2-YL)METHYL)-6-CHLORO-7'-METHOXY-11',12'-DIMETHYL-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[8,16,18,24]TETRAEN]-15'-ONE 13',13'-DIOXIDE. MS (ESI, +ve ion) *m/z* 821.0 $(M+1)^+$.

Example 345

(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(1H-1,2,3-triazol-1-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(1H-1,2,3-triazol-1-ylmethyl)-3,4-dihydro-

2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide



Example 345

Step 1: (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-7'-methylidene-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

A solution of methyltriphenylphosphonium bromide (1.80 g, 5.0 mmol) in THF (15 mL) was cooled to 0 °C. n-butyllithium solution (2.5 M in hexanes, 1.8 mL, 4.5 mmol) was added dropwise and it was stirred at 0 °C for 10 min. The bromide solution was added dropwise to a solution of (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,7'H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7',15'-dione 13',13'-dioxide (0.30 g, 0.50 mmol) in THF (6.0 mL)

(cooled in ice bath) until the yellow color persisted. It was stirred at 0 °C for 12 min. The reaction mixture was added to stirred ice water (20 mL). It was acidified with 1 N HCl to pH 2-4. The organic phase was separated and the aqueous was extracted with EtOAc (50 mL). The organic phase was washed with brine and dried over magnesium sulfate. The filtrate was concentrated to give crude product. The compound was purified by medium pressure chromatography (silica, 0% to 50% EtOAc (+0.3% HOAc:Hexanes) to give (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-7'-methylidene-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (290 mg, 0.49 mmol, 97 % yield). MS (ESI, +ve ion) *m/z* 595.2 $(M+H)^+$.

Step 2: (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(hydroxymethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

The AD-Mix-alpha mixture (640 mg, 0.43 mmol) was dissolved in a 20 mL of a 1:1 mixture of tert-butanol (10.0 mL) and water (10.0 mL) and cooled to 0 °C. The (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-7'-methylidene-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (255 mg, 0.428 mmol) was added and the reaction mixture was warmed slowly to room temperature overnight. Another 5.0 mL of t-BuOH was added to homogenize the mixture. The reaction was stirred overnight. Another 320 mg of AD-Mix-alpha mixture was added and the reaction was stirred for an additional 3 d. The reaction was quenched by adding 575 mg of sodium sulfite at 0 °C and stirring for 45 minutes. The mixture was then extracted with EtOAc (2 x 25 mL). The combined organic layers were washed with brine (1 x 20 mL) and dried over sodium sulfate. The crude product was then purified by medium pressure chromatography (silica, 0% to 100% EtOAc (+0.3%

HOAc):heptanes) to give (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(hydroxymethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (31 mg, 0.049 mmol, 12% yield). MS (ESI, +ve ion) *m/z* 629.2 $(M+H)^+$.

Step 3: ((1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)methyl methanesulfonate

(1S,3'R,6'R,8'E,11'S,12'R)-6-Chloro-7'-hydroxy-7'-(hydroxymethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (25.0 mg, 0.040 mmol) was dissolved in DCM (800 µL) and cooled to 0 °C. Triethylamine (17 µL, 0.12 mmol) was added followed by mesyl chloride (6.50 µL, 0.083 mmol) addition and the reaction was stirred for 1.5 h. The reaction was then diluted with DCM (15 mL) and the mixture was washer with water (2 x 10 mL) and dried over sodium sulfate. The crude product was then purified by medium pressure chromatography (silica, 0% to 70% EtOAc (+0.3% HOAc):heptanes) to give ((1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)methyl methanesulfonate. MS (ESI, +ve ion) *m/z* 707.2 $(M+H)^+$.

Step 4: (1S,3'R,6'R,8'E,11'S,12'R)-7'-(azidomethyl)-6-chloro-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

((1S,3'R,6'R,8'E,11'S,12'R)-6-Chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-

[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)methyl methanesulfonate (10 mg, 0.014 mmol) was dissolved in 0.36 mL of a 5:1 DMF:water mixture. To the solution was added sodium azide (2.1 mg, 3.2 μmol). The mixture was heated to 70 °C and stirred overnight. The reaction was diluted with water and extracted with EtOAc. The organic layer was dried over sodium sulfate and the crude product was purified by medium pressure chromatography (silica, 0% to 60% EtOAc (+0.3%HOAc):heptanes) to give (1S,3'R,6'R,8'E,11'S,12'R)-7'-(azidomethyl)-6-chloro-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (2.1 mg, 3.2 μmol, 23% yield). MS (ESI, +ve ion) *m/z* 654.2 $(M+H)^+$.

Step 5: (1S,3'R,6'R,8'E,11'S,12'R)-7'-(azidomethyl)-6-chloro-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

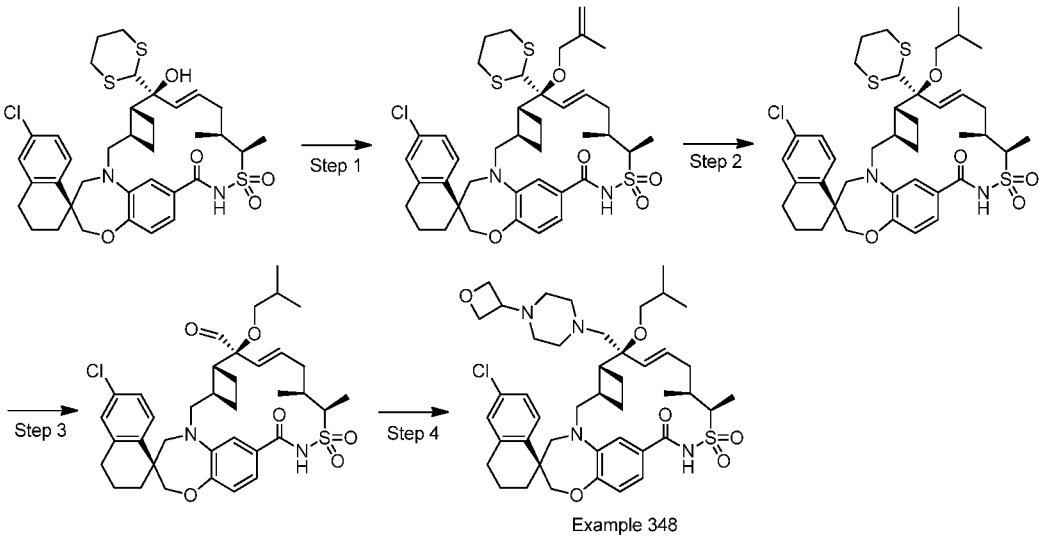
(1S,3'R,6'R,8'E,11'S,12'R)-7'-(Azidomethyl)-6-chloro-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (2.0 mg, 3.1 μmol) was dissolved in 2-methyltetrahydrofuran (1.0 mL) and sodium hydride (60% dispersion) (0.73 mg, 0.031 mmol) was added followed by methyl iodide (0.956 μL, 0.015 mmol). The reaction was then stirred overnight to completion. The reaction was quenched with dropwise additon of water and extracted with EtOAc. The organic layers were then washed with brine and dried over magnesium sulfate to give (1S,3'R,6'R,8'E,11'S,12'R)-7'-(azidomethyl)-6-chloro-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (3.0 mg) that was used directly in the next reaction without any further purification. MS (ESI, +ve ion) *m/z* 668.2 $(M+H)^+$.

Step 6: (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(1H-1,2,3-triazol-1-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(1H-1,2,3-triazol-1-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

(1S,3'R,6'R,8'E,11'S,12'R)-7'-(Azidomethyl)-6-chloro-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (20 mg, 0.030 mmol) was slurried in 3.0 mL of a 1:1:1 t-BuOH:water:DMF solution. To the solution was added copper (II) sulfate (2.9 mg, 0.018 mmol), (+)-sodium l-ascorbate (12.0 mg, 0.061 mmol) and (trimethylsilyl)acetylene (65 µL, 0.46 mmol). The solution was then heated in a microwave reactor at 120 °C for 2 h. The reaction was then diluted with water and EtOAc. The mixture was extracted with EtOAc (2 x 25 mL). The combined organic layers were washed with 1 N lithium chloride solution (1 x 15 mL) and brine (1 x 15 mL) then dried over magnesium sulfate. The residue was then purified by medium pressure chromatography (silica, 25% to 100% EtOAc (+0.3% HOAc):heptanes) to give (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(1H-1,2,3-triazol-1-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(1H-1,2,3-triazol-1-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide. MS (ESI, +ve ion) *m/z* 694.3 $(M+H)^+$.

Example 348

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-7'-(2-methylpropoxy)-7'-((4-(3-oxetanyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide



Example 348

Step 1: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-11',12'-dimethyl-7'-((2-methyl-2-propen-1-yl)oxy)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

The reaction was performed following the procedure for general method 5, step 2. MS (ESI, +ve ion) *m/z* 771.2 $(M+H)^+$.

Step 2: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-11',12'-dimethyl-7'-(2-methylpropoxy)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

The (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-11',12'-dimethyl-7'-((2-methyl-2-propen-1-yl)oxy)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (200 mg, 0.26 mmol) was dissolved in EtOAc (5.0 mL) and platinum (IV) oxide (180 mg, 0.78 mmol) was added. The vessel was then pressurized to 40 psi with hydrogen and stirred for 3.5 h to completion. The black slurry was then filtered through a pad of Celite and washed with EtOAc. The filtrate was then concentrated to give (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-11',12'-dimethyl-7'-(2-methylpropoxy)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (200 mg, 0.26 mmol, 100 % yield). MS (ESI, +ve ion) *m/z* 773.2 $(M+H)^+$.

Step 3: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-7'-(2-methylpropoxy)-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide

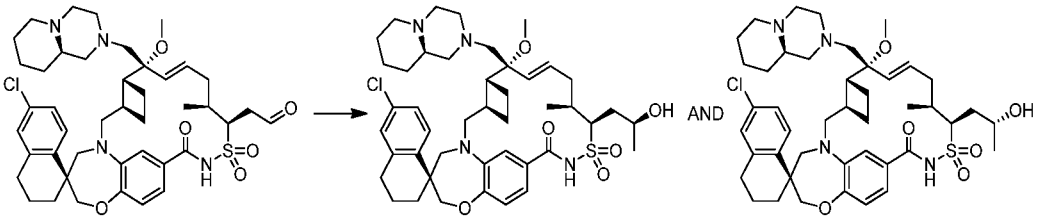
The reaction was performed following the procedure for general method 5, step 3. MS (ESI, +ve ion) *m/z* 683.3 $(M+H)^+$.

Step 4: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-7'-(2-methylpropoxy)-7'-((4-(3-oxetanyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

The reaction was performed following the procedure for general method 8. MS (ESI, +ve ion) *m/z* 809.2 $(M+H)^+$.

Examples 362 and 363

(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-12'-((2S)-2-hydroxypropyl)-7'-methoxy-11'-methyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-12'-((2R)-2-hydroxypropyl)-7'-methoxy-11'-methyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide



Example 360 | Example 362 OR Example 363 | Example 363 OR Example 362

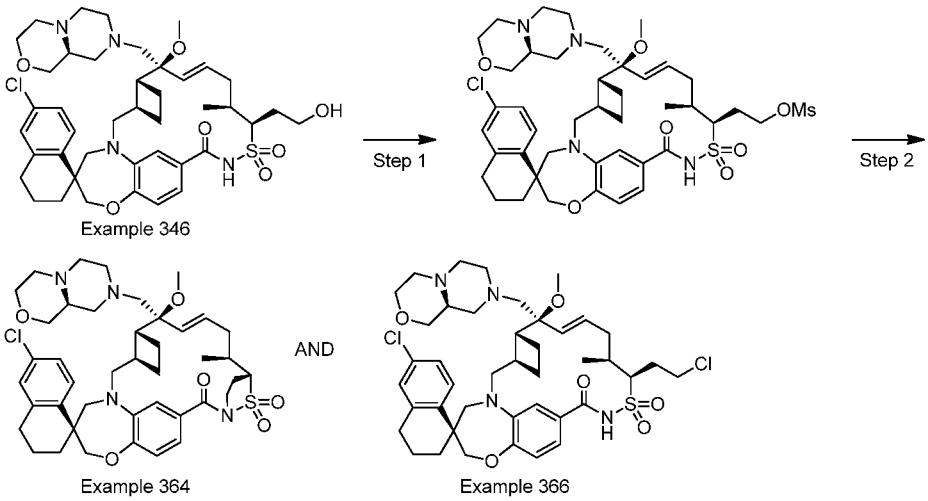
((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-Chloro-7'-methoxy-11'-methyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-12'-yl)acetaldehyde (Example 360) (32 mg, 0.040 mmol) was dissolved in THF (2.0 mL) and cooled to 0 °C. Methylmagnesium bromide (3.4 M in 2-MeTHF, 0.12 mL, 0.40 mmol) was added dropwise and stirred for 45 min. The reaction was quenched with saturated ammonium chloride solution (15 mL) and the mixture was extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with brine (1 x 20 mL) and then dried over sodium sulfate. The mixture was then purified by preparatory SCF chromatography (4FBSA, 250 mm x 21 mm column, Phenomenex, Torrance, CA; 28 g/minute MeOH (+20 mM NH_3) + 42 g/minute CO_2 on Thar 200 SFC; outlet pressure = 100 bar; temperature = 40 °C; wavelength = 220 nm; used 1.1 mL injections of 28 mg/3 mL (9.3

mg/mL) sample solution of MeOH (3 mL) to give (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-12'-((2S)-2-hydroxypropyl)-7'-methoxy-11'-methyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-12'-((2R)-2-hydroxypropyl)-7'-methoxy-11'-methyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (Example 362, first eluting isomer, t_R = 3.19 minutes on analytical SFC; 4FBSA; 40% MeOH (+20 mM NH_3 in CO_2) with >99.5% *de*) (6.2 mg, 7.7 μmol, 19% yield). MS (ESI, +ve ion) *m/z* 809.4 $(M+H)^+$. And (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-12'-((2S)-2-hydroxypropyl)-7'-methoxy-11'-methyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-12'-((2R)-2-hydroxypropyl)-7'-methoxy-11'-methyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (Example 363, second eluting isomer, t_R = 6.49 minutes on analytical SFC; 4FBSA; 40% MeOH (+20 mM NH_3 in CO_2) with >99.5% *de*) (13 mg, 0.016 mmol, 39% yield). MS (ESI, +ve ion) *m/z* 809.4 $(M+H)^+$.

Examples 364 and 366

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-11'-methyl-3,4-dihydro-2H,16'H-spiro[naphthalene-1,23'-[21]oxa[27]thia[1,15]diazapentacyclo[15.7.2.1~12,15~.0~3,6~.0~20,25~]heptacosa[8,17,19,25]tetraen]-16'-one 27',27'-dioxide AND

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-12'-(2-chloroethyl)-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide



Example 346 Example 364 Example 366

Step 1: 2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-11'-methyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-12'-yl)ethyl methanesulfonate

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-Chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-12'-(2-hydroxyethyl)-7'-methoxy-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (Example 346) (15 mg, 0.018 mmol) was dissolved in DCM (1.0 mL) and the Hunig's base (0.011 mL, 0.064 mmol) and mesyl chloride (3.7 μL, 0.048 mmol) were added. The reaction mixture was stirred for 1.5 h to near completion. The mixture was then diluted with DCM (20 mL) and water (15 mL). The layers were separated and the organic layer was dried over sodium sulfate. The filtrate was conentrated to dryness under vacuum

to give 2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-11'-methyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-12'-yl)ethyl methanesulfonate (16 mg, 0.018 mmol, 100% yield) that was used directly in the next reaction. MS (ESI, +ve ion) *m/z* 875.3 $(M+H)^+$.

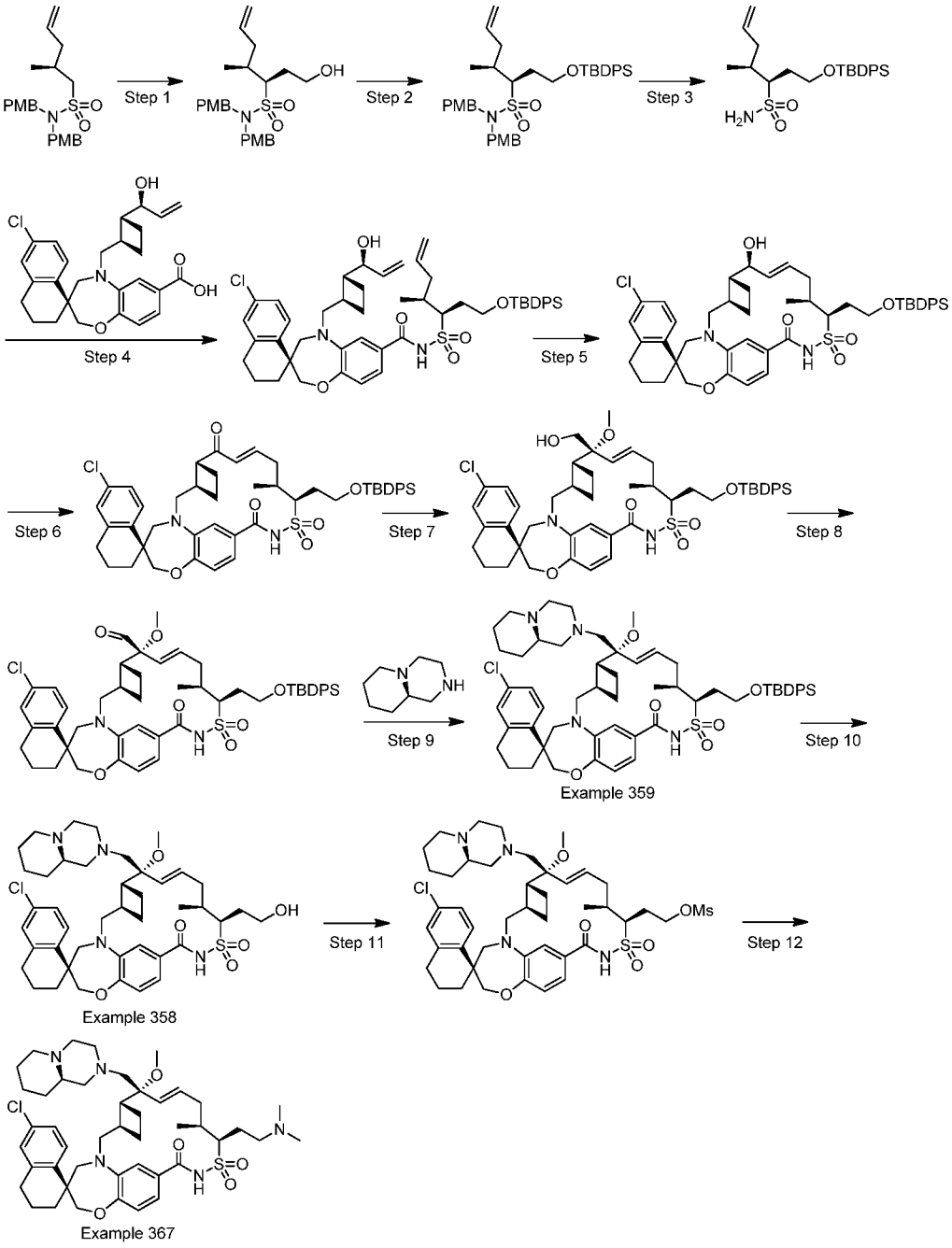
Step 2: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-11'-methyl-3,4-dihydro-2H,16'H-spiro[naphthalene-1,23'-[21]oxa[27]thia[1,15]diazapentacyclo[15.7.2.1~12,15~.0~3,6~.0~20,25~]heptacosa[8,17,19,25]tetraen]-16'-one 27',27'-dioxide AND (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-12'-(2-chloroethyl)-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-Chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-11'-methyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-12'-yl)ethyl methanesulfonate (16 mg, 0.018 mmol) was dissolved in acetonitrile (1.0 mL) and tetrabutylammonium difluoro-triphenylsilicate (59 mg, 0.11 mmol) was added. The reaction was then heated at 75 °C to completion. The reaction was then cooled to room temperature and then diluted with EtOAc (25 mL) and water (20 mL). The layers were separated and the organic layer was washed again with water (1 x 20 mL) and brine (1 x 20 mL) and dried over sodium sulfate. The crude product was then purified by medium pressure chromatography (silica, 0% to 100% (10% 2 M ammonia in MeOH):DCM) to give two products, (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-11'-methyl-

3,4-dihydro-2H,16'H-spiro[naphthalene-1,23'-[21]oxa[27]thia[1,15]diazapentacyclo[15.7.2.1~12,15~.0~3,6~.0~20,25~]heptacosa[8,17,19,25]tetraen]-16'-one 27',27'-dioxide (Example 364) (4.9 mg, 6.3 μmol, 34% yield), MS (ESI, +ve ion) *m/z* 779.3 $(M+H)^+$ AND (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-12'-(2-chloroethyl)-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (Example 366) (3.5 mg, 4.29 μmol, 23% yield), MS (ESI, +ve ion) *m/z* 815.3 $(M+H)^+$.

Examples 358, 359, and 367

(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-12'-(2-hydroxyethyl)-7'-methoxy-11'-methyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (Example 358) AND (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11'-methyl-12'-(2-(((2-methyl-2-propanyl)(diphenyl)silyl)oxy)ethyl)-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (Example 359) AND (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-12'-(2-(dimethylamino)ethyl)-7'-methoxy-11'-methyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (Example 367)



Step 1: (3R,4S)-1-HYDROXY-N,N-BIS(4-METHOXYBENZYL)-4-METHYL-6-HEPTENE-3-SULFONAMIDE

To a solution of (S)-N,N-bis(4-methoxybenzyl)-2-methylpent-4-ene-1-sulfonamide (2.8 g, 6.9 mmol) in THF (15 mL) was added n-butyllithium (2.5 M

in hexanes, 3.1 mL, 7.6 mmol) at -78 °C dropwise. The mixture was stirred at -78 °C for 5 min, and ethylene oxide (2.5 M in THF, 5.6 mL, 14 mmol) was then added. The mixture was allowed to warm up to ambient temperature and stirred for 18 h. The mixture was quenched with saturated aqueous NH_4Cl, and extracted with EtOAc (2X). The organic layer was washed with brine, dried ($MgSO_4$), and filtered. The filtrate was concentrated and the resulting residue was chromatographed (silica gel, 20% to 60%, EtOAc/Hexane) to afford a diasteromeric mixture of the title compound. The mixture was then purified by preparatory SFC chromatography (ChiralPak IC-H 250mm x 30mm column, Phenomenex, Torrance, CA; 35 g/minute MeOH + 105 g/minute CO_2 on Thar 200 SFC; outlet pressure = 100 bar; temperature = 22 °C; wavelength = 215 nm; used 1.0 mL injections of 25,000 mg/50 mL (500 mg/mL) sample solution of MeOH (50mL) to provide (3R,4S)-1-hydroxy-N,N-bis(4-methoxybenzyl)-4-methyl-6-heptene-3-sulfonamide as the slower eluting isomer as a yellow liquid (t_R = 2.51 minutes on analytical SFC; IC-H column; 25% MeOH in CO_2) with 100% *de*. ^{1}H NMR (400 MHz, DICHLOROMETHANE-d2) δ ppm 7.24 (d, J=8.61 Hz, 4H), 6.90 (d, J=8.61 Hz, 4H), 5.62 (ddt, J=16.75, 10.20, 7.07, 7.07 Hz, 1H), 5.08 (s, 1H), 5.05 (br d, J=7.83 Hz, 1H), 4.39 (d, J=15.26 Hz, 2H), 4.23 (d, J=15.26 Hz, 2H), 3.83 (s, 6H), 3.66 – 3.81 (m, 2H), 3.00 – 3.16 (m, 1H), 1.97 – 2.23 (m, 3H), 1.79 – 1.96 (m, 3H), 1.06 (d, J=6.85 Hz, 3H). MS (ESI, +ve ion) *m/z* 470.2 $(M+Na)^+$.

Step 2: (3R,4S)-N,N-bis(4-methoxybenzyl)-4-methyl-1-(((2-methyl-2-propanyl)(diphenyl)silyl)oxy)-6-heptene-3-sulfonamide

(3R,4S)-1-Hydroxy-N,N-bis(4-methoxybenzyl)-4-methylhept-6-ene-3-sulfonamide (6.4 g, 14 mmol) was dissolved in DMF (34 mL). Imidazole (1.7 g, 24 mmol) and tert-butyldiphenylsilyl chloride (6.3 mL, 24 mmol) were added and the mixture was stirred for 45 min. The reaction was then quenched with saturated ammonium chloride solution (150 mL) and extracted with EtOAc (1 x 300 mL). The layers were separated and the organic was washed (1 x 100 mL) with 1 N LiCl solution (1 x 100 mL), 1 N HCl solution and (1 x 100 mL) of brine

and then dried over magnesium sulfate. The crude product was then purified by medium pressure chromatography (silica, 5% to 100% EtOAc:Heptanes) to give (3R,4S)-N,N-bis(4-methoxybenzyl)-4-methyl-1-(((2-methyl-2-propanyl)(diphenyl)silyl)oxy)-6-heptene-3-sulfonamide (9.70 g, 14.14 mmol, 98 % yield). ^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.67 (dt, J=1.5, 7.3 Hz, 4H), 7.47 – 7.35 (m, 6H), 7.16 (d, J=8.8 Hz, 4H), 6.79 – 6.78 (m, 1H), 6.81 (d, J=8.6 Hz, 3H), 5.56 (tdd, J=7.0, 10.1, 17.0 Hz, 1H), 4.97 (dd, J=1.8, 10.0 Hz, 1H), 4.91 (dd, J=1.6, 17.0 Hz, 1H), 4.31 – 4.10 (m, 4H), 3.84 – 3.80 (m, 1H), 3.78 (s, 6H), 3.77 – 3.72 (m, 1H), 3.09 (ddd, J=1.6, 4.2, 7.4 Hz, 1H), 2.22 – 2.07 (m, 2H), 1.98 – 1.79 (m, 3H), 1.07 (s, 9H), 1.02 (d, J=6.8 Hz, 3H). MS (ESI, +ve ion) *m/z* 708.3 $(M+Na)^+$.

Step 3: (3R,4S)-4-methyl-1-(((2-methyl-2-propanyl)(diphenyl)silyl)oxy)-6-heptene-3-sulfonamide

To a 1000 mL flask cooled to 0 °C, was added (3R,4S)-N,N-bis(4-methoxybenzyl)-4-methyl-1-(((2-methyl-2-propanyl)(diphenyl)silyl)oxy)-6-heptene-3-sulfonamide (9.4 g, 14 mmol), DCM (290 mL), anisole (7.5 mL, 69 mmol) and then trifluoroacetic acid (49 mL). The reaction was allowed to warm to room temperature overnight to completion. The reaction mixture was then concentrated on the rotovap to a volume of ~25 mL. The crude product was then purified by medium pressure chromatography (silica, 10% to 50% EtOAc:heptanes) to give (3R,4S)-4-methyl-1-(((2-methyl-2-propanyl)(diphenyl)silyl)oxy)-6-heptene-3-sulfonamide (2.7 g, 6.1 mmol, 44% yield). ^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.67 (ddd, J=1.5, 5.8, 7.2 Hz, 4H), 7.49 – 7.37 (m, 6H), 5.72 (tdd, J=6.9, 10.1, 17.0 Hz, 1H), 5.06 – 4.94 (m, 2H), 4.41 (br s, 2H), 3.93 – 3.80 (m, 2H), 3.23 – 3.16 (m, 1H), 2.46 (m, 1H), 2.13 – 2.06 (m, 1H), 2.05 – 2.01 (m, 1H), 1.91 (dtd, J=3.7, 7.1, 14.7 Hz, 2H), 1.07 (s, 9H), 1.02 (d, J=7.0 Hz, 3H). MS (ESI, +ve ion) *m/z* 468.2 $(M+Na)^+$.

Step 4 : (3S)-6'-chloro-5-(((1R,2R)-2-((1S)-1-hydroxy-2-propen-1-yl)cyclobutyl)methyl)-N-(((3R,4S)-4-methyl-1-(((2-methyl-2-

propanyl)(diphenyl)silyl)oxy)-6-hepten-3-yl)sulfonyl)-3',4,4',5-tetrahydro-2'H-spiro[1,5-benzoxazepine-3,1'-naphthalene]-7-carboxamide

The reaction was performed following the procedure for general method 1 (R^1 = H). MS (ESI, +ve ion) *m/z* 895.3 $(M+H)^+$.

Step 5 : (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11'-methyl-12'-(2-(((2-methyl-2-propanyl)(diphenyl)silyl)oxy)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

The reaction was performed following the procedure for general method 1 (R^1 = H). MS (ESI, +ve ion) *m/z* 867.3 $(M+H)^+$.

Step 6: (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-11'-methyl-12'-(2-(((2-methyl-2-propanyl)(diphenyl)silyl)oxy)ethyl)-3,4-dihydro-2H,7'H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7',15'-dione 13',13'-dioxide

The reaction was performed following the procedure for general method 1 (R^1 = H). MS (ESI, +ve ion) *m/z* 865.3 $(M+H)^+$.

Step 7 : (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(hydroxymethyl)-7'-methoxy-11'-methyl-12'-(2-(((2-methyl-2-propanyl)(diphenyl)silyl)oxy)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

The reaction was performed following the procedure for general method 3 (R^4 = Me). MS (ESI, +ve ion) *m/z* 911.4 $(M+H)^+$.

Step 8 : (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11'-methyl-12'-(2-(((2-methyl-2-propanyl)(diphenyl)silyl)oxy)ethyl)-15'-oxo-3,4-

dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide

The reaction was performed following the procedure for general method 3 (R^4 = Me). MS (ESI, +ve ion) *m/z* 909.3 $(M+H)^+$.

Step 9 : (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11'-methyl-12'-(2-(((2-methyl-2-propanyl)(diphenyl)silyl)oxy)ethyl)-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (Example 359)

The reaction was performed following the procedure for general method 8. MS (ESI, +ve ion) *m/z* 1033.3 $(M+H)^+$.

Step 10 : (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-12'-(2-hydroxyethyl)-7'-methoxy-11'-methyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (Example 358)

(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-Chloro-7'-methoxy-11'-methyl-12'-(2-(((2-methyl-2-propanyl)(diphenyl)silyl)oxy)ethyl)-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (Example 359) (38 mg, 0.037 mmol) was dissolved in THF (1.0 mL). Tetrabutylammonium fluoride (1.0 M in THF, 1.1 mL, 1.1 mmol) was then added and the reaction was stirred for 24 h to completion. The reaction mixture was then diluted with DCM and then loaded directly on a column to purify by medium pressure chromatograhy (silica, 0% to 100% (hold) (10% 2 M ammonia in MeOH:DCM):DCM) to give product that was contaminated with tetrabutylammonium fluoride. This material was then diluted

with water (50 mL) and EtOAc (20 mL). The layers were then separated and the organic layer was then washed again with water (1 x 50 mL) to remove the residual tetrabutylammonium fluoride. The organic layer was then extracted with brine (1 x 15 mL) and dried over sodium sulfate. The slurry was filtered and the filtrate was concentrated to give (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-12'-(2-hydroxyethyl)-7'-methoxy-11'-methyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (Example 358) (150 mg, 0.18 mmol, 61% yield). MS (ESI, +ve ion) *m/z* 795.3 $(M+H)^+$.

Step 11 : 2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11'-methyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-12'-yl)ethyl methanesulfonate

(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-Chloro-12'-(2-hydroxyethyl)-7'-methoxy-11'-methyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (Example 358) (50 mg, 0.063 mmol) was dissolved in DCM (3.0 mL) and the Hunig's Base (66 µL, 0.38 mmol) and mesyl chloride (21 µL, 0.26 mmol) were added. The reaction mixture was stirred for 1.5 h to completion. The mixture was then diluted with DCM (20 mL) and water (25 mL). The layers were separated and the organic layer was washed again with water (25 mL) and then was dried over sodium sulfate. The filtrate was conentrated to dryness under vacuum to give 2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11'-methyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-12'-yl)ethyl methanesulfonate (63 mg). MS (ESI, +ve ion) *m/z* 873.3

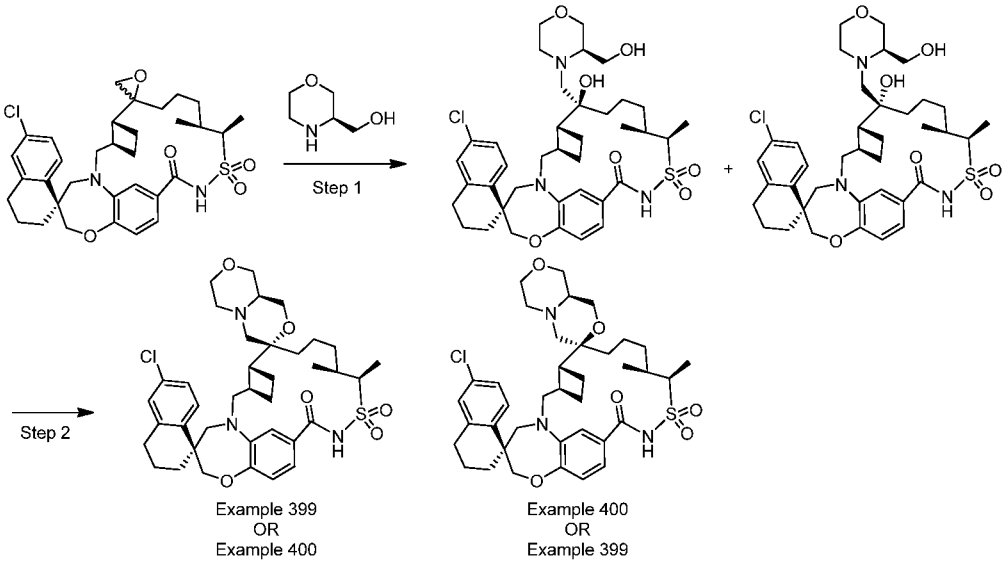
$(M+H)^+$.

Step 12 : (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-12'-(2-(dimethylamino)ethyl)-7'-methoxy-11'-methyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (Example 367)

2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-Chloro-7'-methoxy-11'-methyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-12'-yl)ethyl methanesulfonate (30 mg, 0.34 mmol), dimethylamine (2 M in THF, 0.17 mL, 0.34 mmol), potassium carbonate (95 mg, 0.69 mmol) and a catalytic amount of potassium iodide was dissolved in acetonitrile (1.0 mL) in a vial and sealed with a pressure cap. The reaction mixture was then heated to 65 °C for 40 min to completion. The reaction was then diluted with DCM and filtered through a fine glass frit. The filtrate was then concentrated and the residue was then purified by preparatory SFC chromatography (Kromasil Cyano 250 mm x 21 mm column; 17.5 g/minute MeOH (+20 mM ammonia) + 52.5 g/minute CO_2 on Thar 200 SFC; outlet pressure = 100 bar; temperature = 22 °C; wavelength = 215 nm; used 1.0 mL injections of 31 mg/4 mL (7.8 mg/mL) sample solution of MeOH (4 mL) to give (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-12'-(2-(dimethylamino)ethyl)-7'-methoxy-11'-methyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (Example 367) (4.7 mg, 5.7 mmol, 17% yield) as the slower eluting peak (t_R = 2.90 minutes on analytical SFC; Kromasil Cyano column; 25% MeOH in CO_2) with 97.8% purity. MS (ESI, +ve ion) *m/z* 822.3 $(M+H)^+$.

Examples 399 and 400

(1S,3'R,6'R,7'R,9a''S,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4,6'',7'',9'',9a''-hexahydro-1''H,2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',3''-[1,4]oxazino[3,4-c][1,4]oxazin]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,9a''S,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4,6'',7'',9'',9a''-hexahydro-1''H,2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',3''-[1,4]oxazino[3,4-c][1,4]oxazin]-15'-one 13',13'-dioxide



Step 1: (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-7'-(((3R)-3-(hydroxymethyl)-4-morpholinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-7'-(((3R)-3-(hydroxymethyl)-4-morpholinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide

A glass microwave reaction vessel was charged with (1S,3'R,6'R,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',2''-oxiran]-15'-one 13',13'-dioxide (0.300 g, 0.489 mmol) and 3(R)-hydroxymethylmorpholine (0.650 g, 5.55 mmol; Matrix Sci., Elgin, SC). Ethanol (3 mL) and triethylamine (1.8 mL, 12.9 mmol) were added, the reaction mixture was sealed under argon, and heated in an Initiator microwave reactor at 90 °C for a total of 27 h. The reaction was heated at 90 °C in the microwave for another 16 h. The reaction mixture was purified by reverse-phase HPLC (Gilson; Gemini-NX 10μm, C18, AXIA, 100 x 50 mm column) eluting with 0.1%TFA-H_2O:0.1%TFA CH_3CN (9:1 → 1:9). The fractions containing the desired product were combined and partitioned between pH 7 buffer (1 M K_2HPO_4/KH_2PO_4)/EtOAc. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to give a mixture of (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-7'-(((3R)-3-(hydroxymethyl)-4-morpholinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide and (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-7'-(((3R)-3-(hydroxymethyl)-4-morpholinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide (177 mg, 50%) as a white crystalline solid.

Step 2: (1S,3'R,6'R,7'R,9a''S,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4,6'',7'',9'',9a''-hexahydro-1''H,2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',3''-[1,4]oxazino[3,4-c][1,4]oxazin]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,9a''S,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4,6'',7'',9'',9a''-hexahydro-1''H,2H,15'H-dispiro[naphthalene-1,22'-

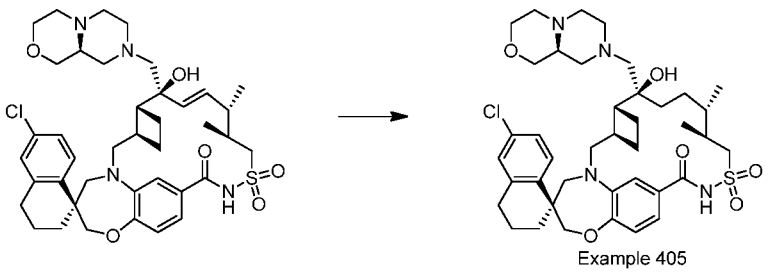
[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',3''-[1,4]oxazino[3,4-c][1,4]oxazin]-15'-one 13',13'-dioxide

To a room temperature mixture of (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-7'-(((3R)-3-(hydroxymethyl)-4-morpholinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide and (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-7'-(((3R)-3-(hydroxymethyl)-4-morpholinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide (0.136 g, 0.186 mmol) in tetrahydrofuran (4 mL) was added sodium hydride, 60% dispersion in mineral oil (0.050 g, 1.250 mmol) and the reaction was stirred for 30 min. To the reaction was added p-toluenesulfonic anhydride (0.250 g, 0.766 mmol) and the reaction was stirred for 5.5 h. To the reaction was added sodium hydride, 60% dispersion in mineral oil (0.050 g, 1.250 mmol) and the reaction was stirred overnight. To the reaction was added p-toluenesulfonic anhydride (0.180 g) and the reaction was stirred for 24 h. To the reaction was added sodium hydride, 60% dispersion in mineral oil (0.050 g, 1.25 mmol) and the reaction was stirred for another 24 h. The reaction was quenched with pH 7 buffer (1 M K_2HPO_4/KH_2PO_4) and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine and the filtrate was purified by reverse-phase HPLC (Gilson; Gemini-NX 10 μm, C18, AXIA, 100 x 50 mm column) eluting with 0.1%TFA-H_2O:0.1%TFA CH_3CN (9:1 → 1:9). The fractions containing the desired product were combined and partitioned between pH 7 buffer (1 M K_2HPO_4/KH_2PO_4)/EtOAc. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to give 118 mg (89%) of a white solid. The material was purified by achiral SFC chromatography to give (1S,3'R,6'R,7'R,9a''S,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4,6'',7'',9'',9a''-

hexahydro-1''H,2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',3''-[1,4]oxazino[3,4-c][1,4]oxazin]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,9a''S,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4,6'',7'',9'',9a''-hexahydro-1''H,2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',3''-[1,4]oxazino[3,4-c][1,4]oxazin]-15'-one 13',13'-dioxide (10 mg, 8%, first eluted peak) as a white crystalline solid. *m/z* (ESI, +ve ion) 712.7 $(M+1)^+$. A second eluting compound was isolated as (1S,3'R,6'R,7'R,9a''S,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4,6'',7'',9'',9a''-hexahydro-1''H,2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',3''-[1,4]oxazino[3,4-c][1,4]oxazin]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,9a''S,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4,6'',7'',9'',9a''-hexahydro-1''H,2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',3''-[1,4]oxazino[3,4-c][1,4]oxazin]-15'-one 13',13'-dioxide (12 mg, 9%, second eluted peak) as a white crystalline solid. (ESI, +ve ion) *m/z* 712.6 $(M+1)^+$.

Example 405

(1S,3'R,6'R,7'S,10'S,11'S)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-hydroxy-10',11'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide

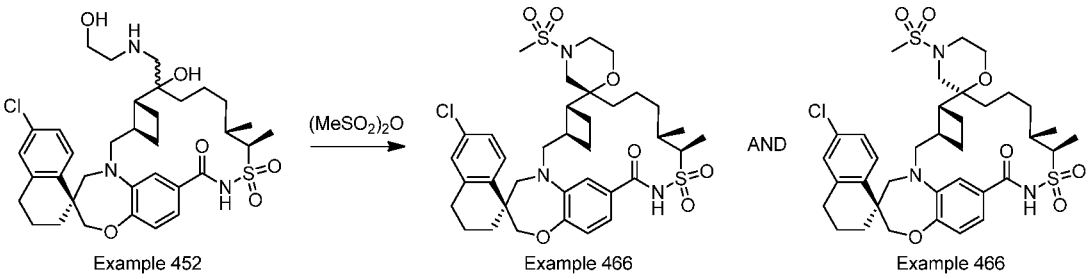


Example 405

A vial was charged with (1S,3'R,6'R,7'S,8'E,10'S,11'S)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-hydroxy-10',11'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (0.012 g, 0.016 mmol) and platinum (IV) oxide (0.4 mg, 1.6 µmol). Ethanol (2 mL) and methanol (0.3 mL) were added. The reaction was flushed with nitrogen for 5 min then evacuated / backfilled with hydrogen three times. The reaction was stirred under 20 psi hydrogen at room temperature overnight. The reaction was flushed with nitrogen. Methanol (5 mL) and DCM (5 mL) were added. The reaction was flushed with nitrogen then evacuated / backfilled with hydrogen three times. The reaction was stirred under 20 psi hydrogen at room temperature for 24 h. The reaction was flushed with nitrogen and filtered through celite rinsing with ethyl acetate. The filtrate was concentrated under reduced pressure and purified by silica gel flash chromatography using a graident of 0% to 10% MeOH in DCM to afford the title compound (0.007 g, 9 µmol, 58% yield). MS (ESI, +ve ion) *m/z* 755.2 $(M+H)^+$.

Example 466

(1S,3'R,6'R,7'R,11'S,12'R)-6-CHLORO-11',12'-DIMETHYL-4''-(METHYLSULFONYL)-3,4-DIHYDRO-2H,15'H-DISPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[16,18,24]TRIENE-7',2''-[1,4]OXAZINAN]-15'-ONE 13',13'-DIOXIDE AND (1S,3'R,6'R,7'S,11'S,12'R)-6-CHLORO-11',12'-DIMETHYL-4''-(METHYLSULFONYL)-3,4-DIHYDRO-2H,15'H-DISPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[16,18,24]TRIENE-7',2''-[1,4]OXAZINAN]-15'-ONE 13',13'-DIOXIDE



Example 452 Example 466 Example 466

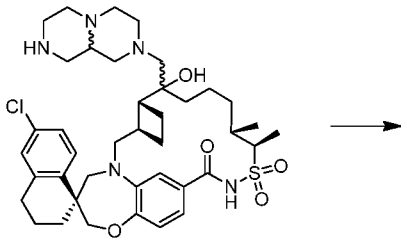
To a stirred solution of (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-7'-(((2-hydroxyethyl)amino)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-7'-(((2-hydroxyethyl)amino)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide (Example 452) (34 mg, 0.043 mmol) in THF (1.5 mL) in a microwave reaction vessel was added at room temperature, diisopropylethylamine (0.075 mL, 0.431 mmol) under argon followed by methanesulfonic anhydride (37.6 mg, 0.216 mmol). The resulting mixture was stirred at room temperature for 5 min during which the color of the mixture changed from colorless to light greenish yellow. The vessel was capped and subjected to microwave reaction irradiation (3 h at 70 °C). 4-(Dimethylamino)pyridine (15.81 mg, 0.129 mmol) was then added followed by more methanesulfonic anhydride (18 mg, 0.11 mmol). The vessel was sealed and again subjected to microwave irradiation (4 h at 70 °C). The volatiles were removed and the concentrate was dissolved in DMSO and purified by preparative reverse-phase HPLC (Gemini™ Prep C18 5 μm column; Phenomenex, Torrance, CA; gradient elution of 30% to 95% MeCN in water, where both solvents contain 0.1% TFA, 25 min method) to provide, after lyophilization, 4.0 mg of (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-11',12'-dimethyl-4''-(methylsulfonyl)-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24

]triene-7',2''-[1,4]oxazinan]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-11',12'-dimethyl-4''-(methylsulfonyl)-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',2''-[1,4]oxazinan]-15'-one 13',13'-dioxide as a white solid. MS (ESI, +ve ion) *m/z* 734.2 $(M+1)^+$.

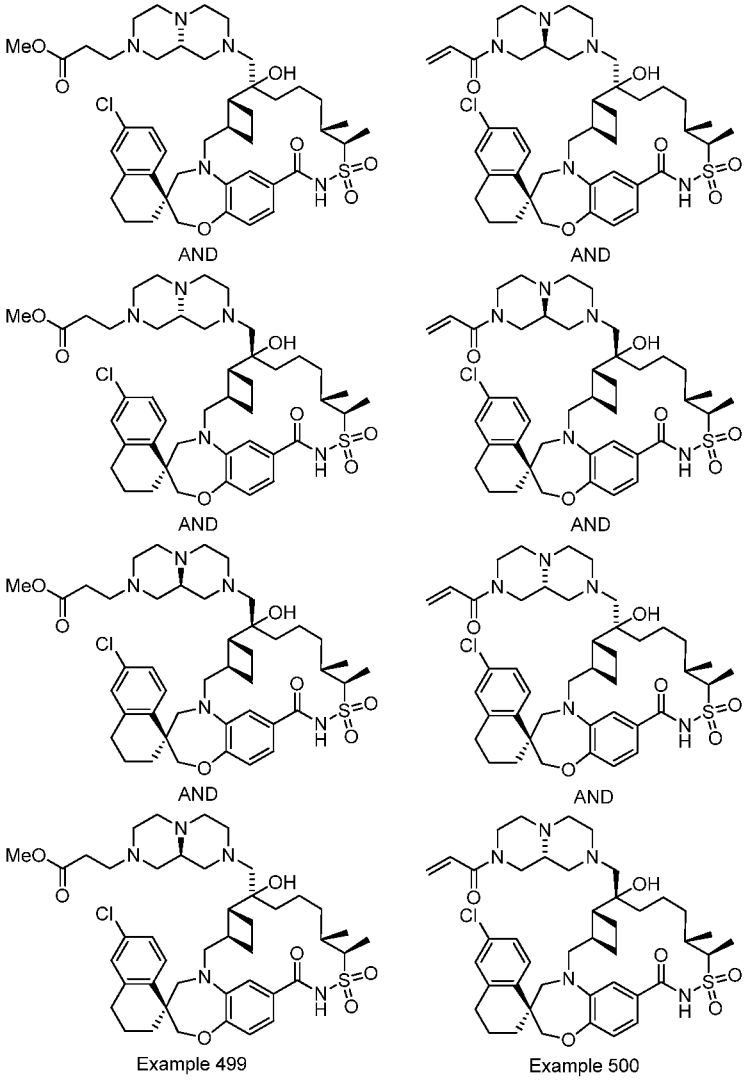
Examples 499 and 500

METHYL 3-((9AR)-8-(((1S,3'R,6'R,7'R,11'S,12'R)-6-CHLORO-7'-HYDROXY-11',12'-DIMETHYL-13',13'-DIOXIDO-15'-OXO-3,4-DIHYDRO-2H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[16,18,24]TRIEN]-7'-YL)METHYL)OCTAHYDRO-2H-PYRAZINO[1,2-A]PYRAZIN-2-YL)PROPANOATE AND METHYL 3-((9AR)-8-(((1S,3'R,6'R,7'S,11'S,12'R)-6-CHLORO-7'-HYDROXY-11',12'-DIMETHYL-13',13'-DIOXIDO-15'-OXO-3,4-DIHYDRO-2H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[16,18,24]TRIEN]-7'-YL)METHYL)OCTAHYDRO-2H-PYRAZINO[1,2-A]PYRAZIN-2-YL)PROPANOATE AND METHYL 3-((9AS)-8-(((1S,3'R,6'R,7'R,11'S,12'R)-6-CHLORO-7'-HYDROXY-11',12'-DIMETHYL-13',13'-DIOXIDO-15'-OXO-3,4-DIHYDRO-2H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[16,18,24]TRIEN]-7'-YL)METHYL)OCTAHYDRO-2H-PYRAZINO[1,2-A]PYRAZIN-2-YL)PROPANOATE AND METHYL 3-((9AS)-8-(((1S,3'R,6'R,7'S,11'S,12'R)-6-CHLORO-7'-HYDROXY-11',12'-DIMETHYL-13',13'-DIOXIDO-15'-OXO-3,4-DIHYDRO-2H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[16,18,24]TRIEN]-7'-YL)METHYL)OCTAHYDRO-2H-

PYRAZINO[1,2-A]PYRAZIN-2-YL)PROPANOATE (Example 499) AND (1S,3'R,6'R,7'R,11'S,12'R)-7'-(((9AR)-8-ACRYLOYLOCTAHYDRO-2H-PYRAZINO[1,2-A]PYRAZIN-2-YL)METHYL)-6-CHLORO-7'-HYDROXY-11',12'-DIMETHYL-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[16,18,24]TRIEN]-15'-ONE 13',13'-DIOXIDE AND (1S,3'R,6'R,7'R,11'S,12'R)-7'-(((9AS)-8-ACRYLOYLOCTAHYDRO-2H-PYRAZINO[1,2-A]PYRAZIN-2-YL)METHYL)-6-CHLORO-7'-HYDROXY-11',12'-DIMETHYL-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[16,18,24]TRIEN]-15'-ONE 13',13'-DIOXIDE AND (1S,3'R,6'R,7'S,11'S,12'R)-7'-(((9AR)-8-ACRYLOYLOCTAHYDRO-2H-PYRAZINO[1,2-A]PYRAZIN-2-YL)METHYL)-6-CHLORO-7'-HYDROXY-11',12'-DIMETHYL-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[16,18,24]TRIEN]-15'-ONE 13',13'-DIOXIDE AND (1S,3'R,6'R,7'S,11'S,12'R)-7'-(((9AS)-8-ACRYLOYLOCTAHYDRO-2H-PYRAZINO[1,2-A]PYRAZIN-2-YL)METHYL)-6-CHLORO-7'-HYDROXY-11',12'-DIMETHYL-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[16,18,24]TRIEN]-15'-ONE 13',13'-DIOXIDE (Example 500)



Example 479



Example 499 Example 500

To a stirred solution of (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((9aR)-octahydro-2H-pyrazino[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-

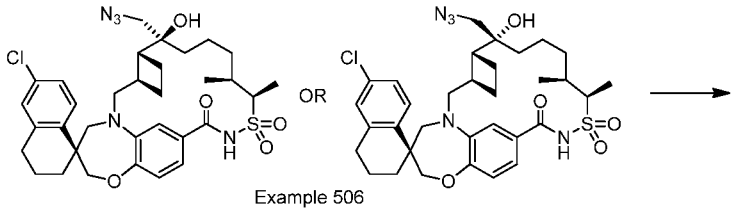
[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((9aS)-octahydro-2H-pyrazino[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((9aR)-octahydro-2H-pyrazino[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((9aS)-octahydro-2H-pyrazino[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide (Example 479) (0.15 g, 0.199 mmol) and diisopropylethylamine (1.5 mL, 8.62 mmol) in DCM (10 mL) was added at room temperature acrylic acid n-hydroxysuccinimide ester (0.303 g, 1.789 mmol) in one portion as a solid. The resulting mixture was stirred at room temperature for 3 h. MeOH (8 mL) was added to the reaction mixture. The resulting mixture was stirred at room temperature for 20 min before concentrated in vacuo. The crude residue was directly loaded onto a silica gel precolumn (25 g) and subjected to combi-flash column chromatography on a 12 g ISCO gold column eluting with 1% to 20% MeOH/DCM to give 30 mg of impure product mixture, which was subjected to preparative reverse-phase HPLC (Gemini™ Prep C18 10 µm column; Phenomenex, Torrance, CA; gradient elution of 20% to 90% MeCN in water, where both solvents contain 0.1% TFA, a 15-min gradient in a 24-min method) to give, after lyophilization, 18.5 mg of METHYL 3-((9AR)-8-(((1S,3'R,6'R,7'R,11'S,12'R)-6-CHLORO-7'-HYDROXY-11',12'-DIMETHYL-13',13'-DIOXIDO-15'-OXO-3,4-DIHYDRO-2H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENT

ACOSA[16,18,24]TRIEN]-7'-YL)METHYL)OCTAHYDRO-2H-PYRAZINO[1,2-A]PYRAZIN-2-YL)PROPANOATE AND METHYL 3-((9AR)-8-(((1S,3'R,6'R,7'S,11'S,12'R)-6-CHLORO-7'-HYDROXY-11',12'-DIMETHYL-13',13'-DIOXIDO-15'-OXO-3,4-DIHYDRO-2H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[16,18,24]TRIEN]-7'-YL)METHYL)OCTAHYDRO-2H-PYRAZINO[1,2-A]PYRAZIN-2-YL)PROPANOATE AND METHYL 3-((9AS)-8-(((1S,3'R,6'R,7'R,11'S,12'R)-6-CHLORO-7'-HYDROXY-11',12'-DIMETHYL-13',13'-DIOXIDO-15'-OXO-3,4-DIHYDRO-2H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[16,18,24]TRIEN]-7'-YL)METHYL)OCTAHYDRO-2H-PYRAZINO[1,2-A]PYRAZIN-2-YL)PROPANOATE AND METHYL 3-((9AS)-8-(((1S,3'R,6'R,7'S,11'S,12'R)-6-CHLORO-7'-HYDROXY-11',12'-DIMETHYL-13',13'-DIOXIDO-15'-OXO-3,4-DIHYDRO-2H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[16,18,24]TRIEN]-7'-YL)METHYL)OCTAHYDRO-2H-PYRAZINO[1,2-A]PYRAZIN-2-YL)PROPANOATE (EXAMPLE 499) in an approximately 1-to-1-to-1-to-1 epimeric mixture. MS (ESI, +ve ion) *m/z* 841.0 $(M+1)^+$. In addition, (1S,3'R,6'R,7'R,11'S,12'R)-7'-(((9AR)-8-ACRYLOYLOCTAHYDRO-2H-PYRAZINO[1,2-A]PYRAZIN-2-YL)METHYL)-6-CHLORO-7'-HYDROXY-11',12'-DIMETHYL-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[16,18,24]TRIEN]-15'-ONE 13',13'-DIOXIDE AND (1S,3'R,6'R,7'R,11'S,12'R)-7'-(((9AS)-8-ACRYLOYLOCTAHYDRO-2H-PYRAZINO[1,2-A]PYRAZIN-2-YL)METHYL)-6-CHLORO-7'-HYDROXY-11',12'-DIMETHYL-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENT

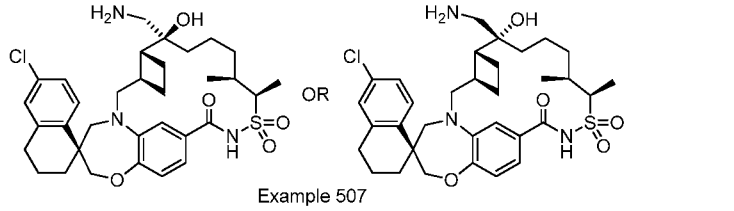
ACOSA[16,18,24]TRIEN]-15'-ONE 13',13'-DIOXIDE AND (1S,3'R,6'R,7'S,11'S,12'R)-7'-(((9AR)-8-ACRYLOYLOCTAHYDRO-2H-PYRAZINO[1,2-A]PYRAZIN-2-YL)METHYL)-6-CHLORO-7'-HYDROXY-11',12'-DIMETHYL-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[16,18,24]TRIEN]-15'-ONE 13',13'-DIOXIDE AND (1S,3'R,6'R,7'S,11'S,12'R)-7'-(((9AS)-8-ACRYLOYLOCTAHYDRO-2H-PYRAZINO[1,2-A]PYRAZIN-2-YL)METHYL)-6-CHLORO-7'-HYDROXY-11',12'-DIMETHYL-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[16,18,24]TRIEN]-15'-ONE 13',13'-DIOXIDE (EXAMPLE 500) was isolated as a white solid in a 1-to-1-to-1-to-1 epimeric mixture. MS (ESI, +ve ion) *m/z* 808.8 $(M+1)^+$.

Example 507

(1S,3'R,6'R,7'S,11'S,12'R)-7'-(aminomethyl)-6-chloro-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-7'-(aminomethyl)-6-chloro-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide



Example 506



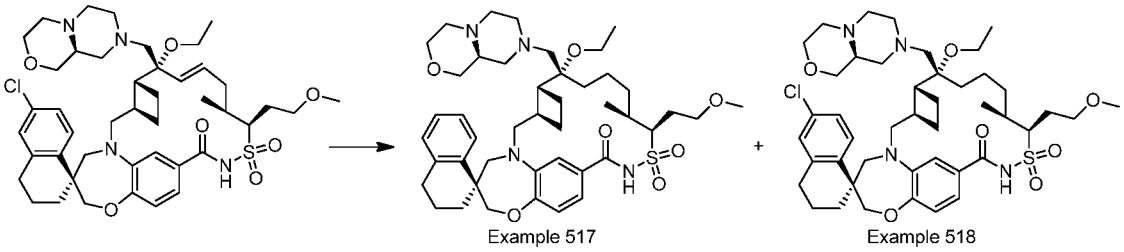
Example 507

(1S,3'R,6'R,7'S,11'S,12'R)-7'-(Azidomethyl)-6-chloro-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6.0~19,24]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-7'-(azidomethyl)-6-chloro-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6.0~19,24]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide (Example 506) (36.0 mg, 0.055 mmol) was dissolved in ethyl acetate (5.0 mL) and platinum(IV) oxide (2.49 mg, 11.0 μmol) was added. The reaction vessel was filled with hydrogen to 15 psi and stirred vigorously for 2.5 h. MeOH (1.5 mL) was added and the reaction vessel was again filled with hydrogen (15 psi) and stirred overnight. The slurry was filtered and the preciptiate was washed with DMSO to ensure that no product was remaining on the catalyst. The filtrate was concentrated. The crude material was purified by reverse-phase preparative HPLC using a Phenomenex Gemini column, 10 μm, C18, 100 Å, 150 x 30 mm, 0.1% TFA in CH_3CN/H_2O, gradient 20% to 85% over 30 min to provide (1S,3'R,6'R,7'S,11'S,12'R)-7'-(aminomethyl)-6-chloro-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-7'-(aminomethyl)-6-chloro-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-

[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide (32 mg, 0.037 mmol, 68% yield) as a di-TFA salt. MS (ESI, +ve ion) *m/z* 630.2 $(M+H)^+$.

Examples 517 and 518

(1S,3'R,6'R,7'R,11'S,12'R)-7'-ethoxy-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-ethoxy-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide

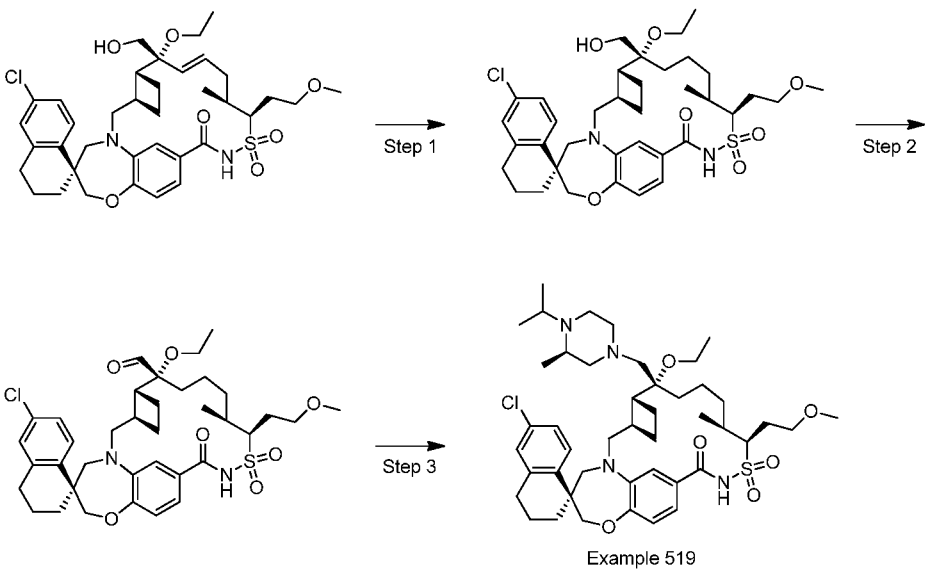


A reaction vessel was charged with platinum (IV) oxide (18.6 mg, 0.082 mmol), then placed in a Biotage Endeavor and treated with a solution of (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (128 mg) in EtOAc (3 mL). The vessel was purged with Ar (3X), then pressurized to 200 psi with H_2 and stirred (250 RPM) at 80 °C for 20 h. The vessel was cooled to room temperature and purged with Ar (3X), then filtered through a celite pad that was rinsed liberally with EtOAc. The filtrate was concentrated in vacuo and purified by reverse-phase preparative

HPLC (Shimadzu) on a Phenomenex Luna column (5 μm, C18, 110 Å, Axia, 150 mm X 21.2 mm) eluting at 30 mL/min with a linear gradient of 25% to 100% MeCN (0.1% TFA) in water (0.1% TFA) over 20 min. The desired fractions were poured into 10% Na_2CO_3 and extracted with DCM (2 X 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to afford (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-ethoxy-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide (Example 518) (32.8 mg, 0.040 mmol, 13% yield) as a white solid. MS (ESI, +ve ion) *m/z* 827.2 $(M+H)^+$. In addition, (1S,3'R,6'R,7'R,11'S,12'R)-7'-ethoxy-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide (Example 517) was isolated as an earlier eluting peak (12.9 mg, 0.016 mmol, 6% yield) as a white solid. MS (ESI, +ve ion) *m/z* 793.3 $(M+H)^+$.

Example 519

(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-ethoxy-12'-(2-methoxyethyl)-11'-methyl-7'-(((3R)-3-methyl-4-(2-propanyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide



Example 519

Step 1: (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-ethoxy-7'-(hydroxymethyl)-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide

A reaction vessel was charged with sulfided Pt on carbon (5% wt%, 54.2 mg, 0.295 mmol), then placed in the Biotage Endeavor and treated with a solution of (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-7'-(hydroxymethyl)-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide [derived from methods analogous to General Method 3, steps 1-2 using (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,7'H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7',15'-dione 13',13'-dioxide] (207 mg, 0.295 mmol) in EtOAc (3.25 mL). The vessel was purged with Ar (3X), then pressurized to 200 psi with H_2 and stirred (250 RPM) at 80 °C for 20 h. The vessel was cooled to room temperature and purged with Ar (3X), then filtered through a celite pad that was rinsed liberally with EtOAc. The filtrate was concentrated in vacuo to afford

(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-ethoxy-7'-(hydroxymethyl)-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide (196 mg, 0.279 mmol, 94% yield) as a white solid. MS (ESI, +ve ion) *m/z* 703.3 $(M+H)^+$.

Step 2: (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-ethoxy-12'-(2-methoxyethyl)-11'-methyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene]-7'-carbaldehyde 13',13'-dioxide

To an ice bath cooled solution of (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-ethoxy-7'-(hydroxymethyl)-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide (161 mg, 0.229 mmol) in DCM (10 mL) was added 0.3 M Dess-Martin Periodinane in DCM (1.0 mL, 0.300 mmol) dropwise over 2 min. After 1.5 h, LC-MS suggests about 60% conversion, the reaction was treated with another 0.9 mL of 0.3 M Dess-Martin Periodinane in DCM dropwise over 1 min. After a further 2.5 h, LC-MS suggests complete conversion. The reaction was treated with 5 mL of saturated sodium bisulfite and stirred for 20 min. The reaction was poured into water (15 mL) and the organic layer separated. The aqeuous layer was extracted with DCM (1 X 5 mL). The combined organic layers were concentrated in vacuo and adsorbed onto a plug of silica gel and chromatographed through a Redi-Sep® pre-packed silica gel column (Gold, 12 g), eluting with 0% to 25% EtOAc in heptanes, to afford (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-ethoxy-12'-(2-methoxyethyl)-11'-methyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene]-7'-carbaldehyde 13',13'-dioxide (105 mg, 0.150 mmol, 65.4 % yield) as a white solid. MS (ESI, +ve ion) *m/z* 701.2 $(M+H)^+$.

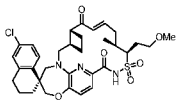
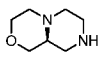
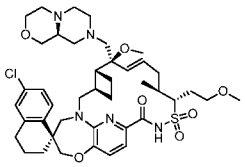
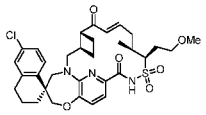
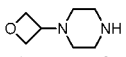
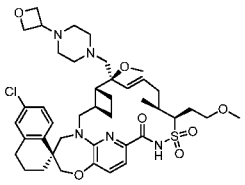
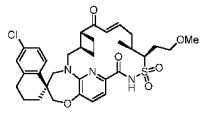
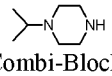
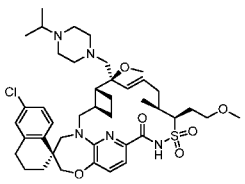
Step 3: (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-ethoxy-12'-(2-methoxyethyl)-11'-methyl-7'-(((3R)-3-methyl-4-(2-propanyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide

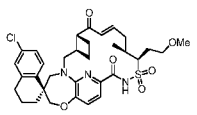
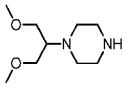
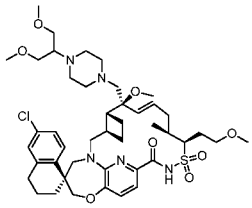
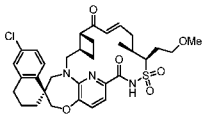
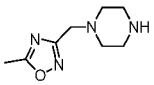
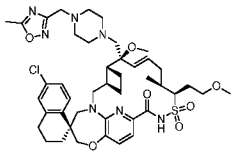
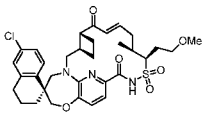
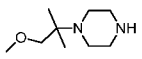
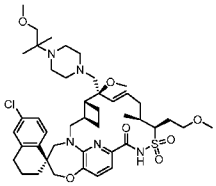
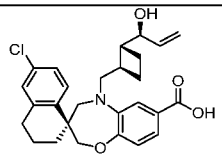
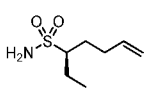
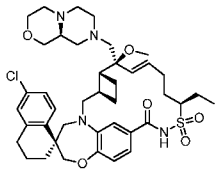
To a round bottom flask was charged the TFA salt of (R)-1-isopropyl-2-methylpiperazine (68.2 mg, 0.285 mmol) and (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-ethoxy-12'-(2-methoxyethyl)-11'-methyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene]-7'-carbaldehyde 13',13'-dioxide (50 mg, 0.071 mmol) in DCE (2 mL) and N,N-diisopropylethylamine (0.1 mL, 0.574 mmol). After 1.5 h, the solution was treated with sodium triacetoxyborohydride (6 mg). After a further 3 h, the reaction was treated with more sodium triacetoxyborohydride (7 mg). After a further 16 h, the reaction was again treated with sodium triacetoxy borohydride (6 mg). The reaction was monitored by LC-MS and sodium triacetoxyborohydride added in 5-10 mg portions until reaction was judged complete. After a further 24 h, the reaction was diluted with DCE (3 mL). After 4 d, the reaction was treated with acetic acid (12 μL, 0.208 mmol). After a further 24 h, more acetic acid (18 μL) was added. After a further 24 h, the reaction was treated with another 30 mg of amine. After a further 96 h, the reaction was treated with larger portions of sodium triacetoxyborohydride to drive reaction to desired product or the alcohol resulting from reduced aldehyde. LC-MS suggests no further progress, the reaction was quenched with water and the aqeuous layer extracted with DCM (2 X 10 mL). The combined DCM layers were concentrated in vacuo and adsorbed onto a plug of silica gel and chromatographed through a Redi-Sep® pre-packed silica gel column (Gold, 12 g), eluting with 0% to 80% EtOAc:EtOH (3:1) in heptanes, to afford (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-ethoxy-12'-(2-methoxyethyl)-11'-methyl-7'-(((3R)-3-methyl-4-(2-propanyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-

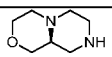
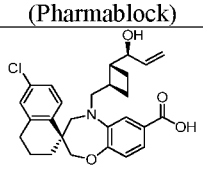
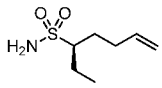
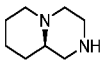
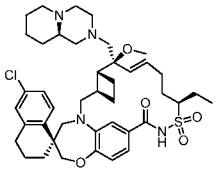
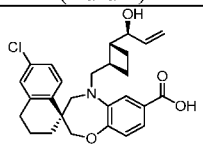
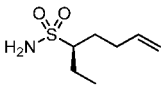
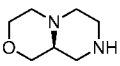
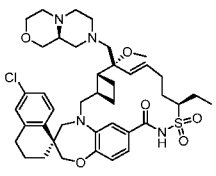
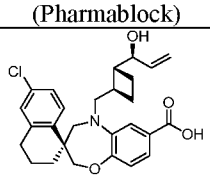
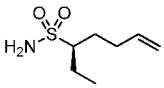
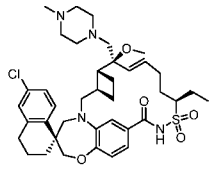
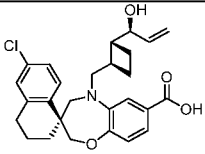
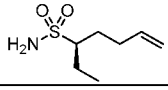
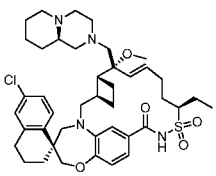
[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide (24.2 mg, 0.029 mmol, 41.0 % yield) as a white solid. MS (ESI, +ve ion) *m/z* 827.4 $(M+H)^+$.

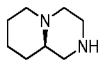
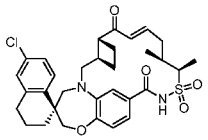
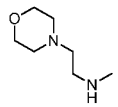
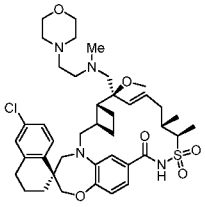
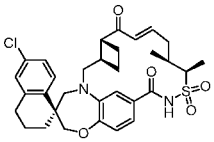
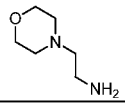
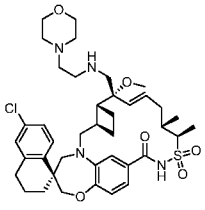
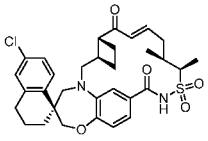
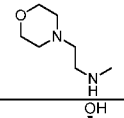
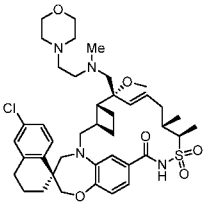
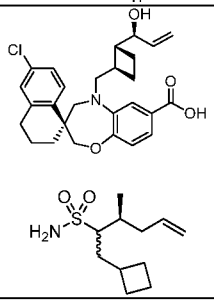
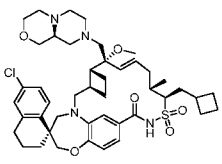
Table 1 lists compounds prepared by the General Methods outlined in the present specification.

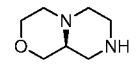
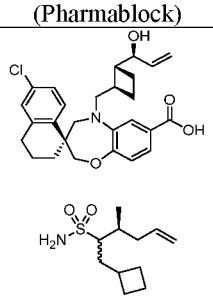
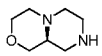
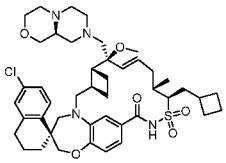
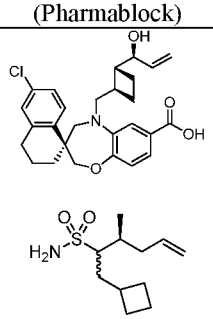
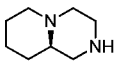
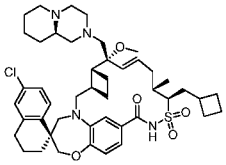
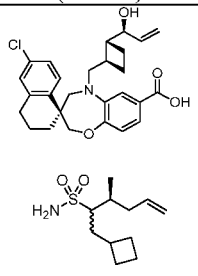
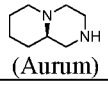
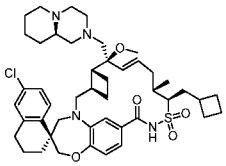
TABLE 1: Examples Prepared by the General Methods

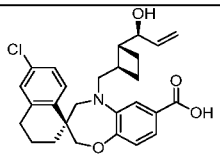
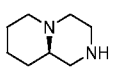
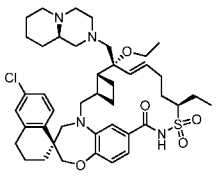
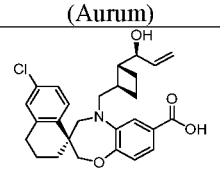
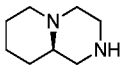
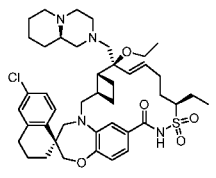
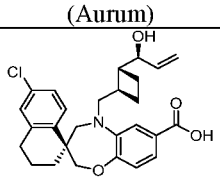
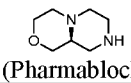
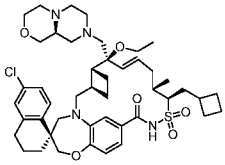
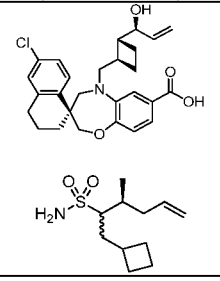
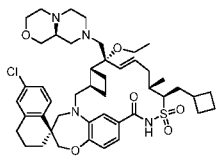
Example Number	Starting Materials	General Method	Product Structure	Product Name	MS Data $(M+1)^+$
22	 MeI  (Pharmablock)	5, 12		(1S,3'R,6'R,7'S,8'E,11'S,12'S)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	812.4
23	 MeI  (Asta Tech)	5, 12		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-7'-((4-(3-oxetanyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	812.2
24	 MeI  (Combi-Blocks)	5, 12		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-7'-((4-(1-methylethyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16	798.2

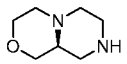
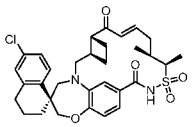
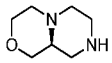
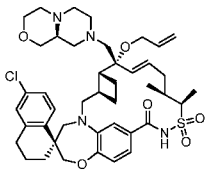
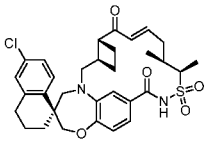
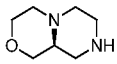
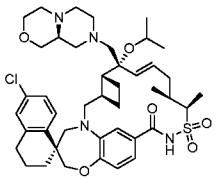
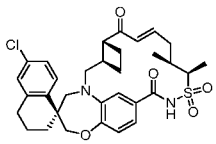
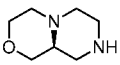
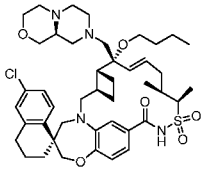
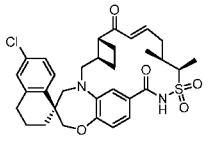
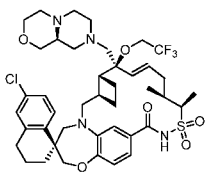
				,18,24]tetraen]-15'-one 13',13'-dioxide	
25	 MeI  (FCH Group)	5, 12		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-12'-(2-methoxyethyl)-7'-((4-(2-methoxy-1-(methoxymethyl)ethyl)-1-piperazinyl)methyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	858.4
26	 MeI  (Enanime)	5, 12		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-7'-((4-((5-methyl-1,2,4-oxadiazol-3-yl)methyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	852.4
27	 MeI 	5, 12		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-7'-((4-(2-methoxy-1,1-dimethylethyl)-1-piperazinyl)methyl)-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	842.4
28	  MeI	1 (R^1 = H), 5, 8		(1S,3'R,6'R,7'S,8'E,12'R)-6-chloro-12'-ethyl-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,	767.2

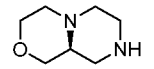
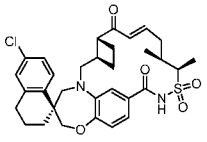
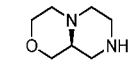
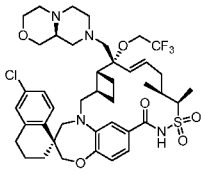
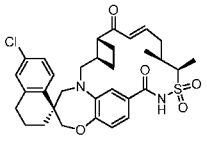
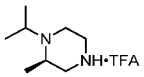
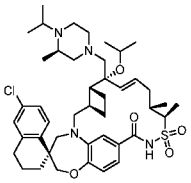
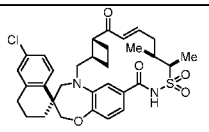
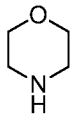
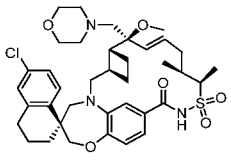
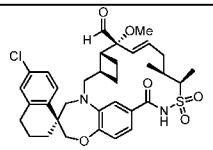
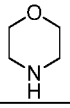
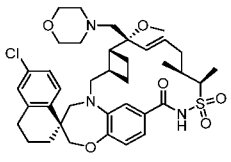
	 (Pharmablock)			24]tetraen]-15'-one 13',13'-dioxide	
29	  MeI  (Aurum)	1 (R^1 = H), 5, 8		(1S,3'R,6'R,7'S,8'E,12'R)-6-chloro-12'-ethyl-7'-methoxy-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	765.2
30	  MeI  (Pharmablock)	1 (R^1 = H), 5, 8		(1S,3'R,6'R,7'R,8'E,12'R)-6-chloro-12'-ethyl-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	767.2
31	  MeI	1 (R^1 = H), 5, 8		(1S,3'R,6'R,7'S,8'E,12'R)-6-chloro-12'-ethyl-7'-methoxy-7'-((4-methyl-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	725.2
32	 	1 (R^1 = H), 5, 8		(1S,3'R,6'R,7'R,8'E,12'R)-6-chloro-12'-ethyl-7'-methoxy-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~	765.2

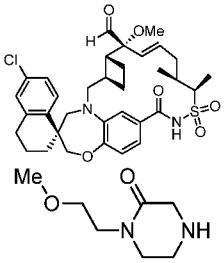
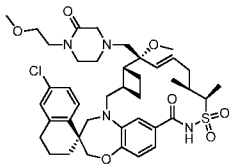
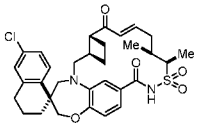
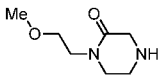
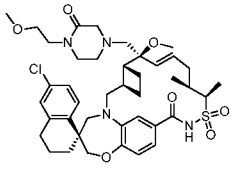
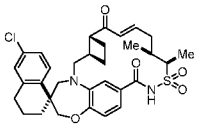
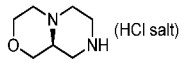
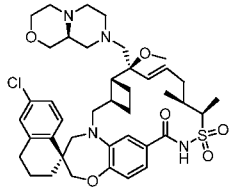
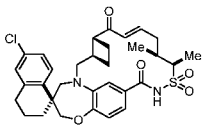
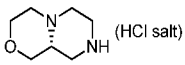
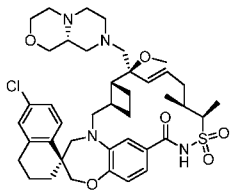
	MeI  (Aurum)			19,24~]pentacosa[8,16,18, 24]tetraen]-15'-one 13',13'-dioxide	
35	 MeI 	5, 8		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((methyl(2-(4-morpholinyl)ethyl)amino) methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18, 24]tetraen]-15'-one 13',13'-dioxide	769.2
36	 MeI 	5, 13		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((2-(4-morpholinyl)ethyl)amino) methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18, 24]tetraen]-15'-one 13',13'-dioxide	755.2
37	 MeI 	5, 13		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((methyl(2-(4-morpholinyl)ethyl)amino) methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18, 24]tetraen]-15'-one 13',13'-dioxide	769.2
38		2, 5, 8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-12'-(cyclobutylmethyl)-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-	821.2

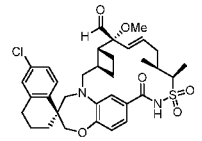
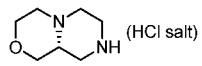
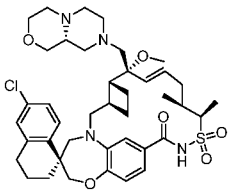
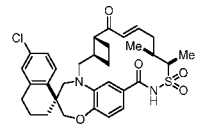
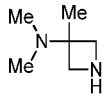
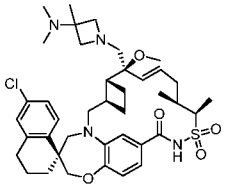
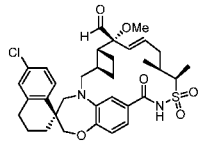
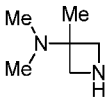
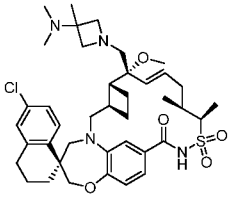
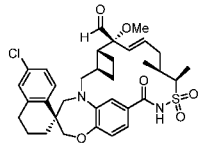
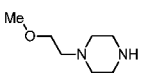
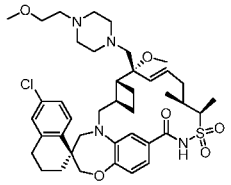
	MeI  (Pharmablock)			[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
39	 MeI  (Pharmablock)	2, 5, 8		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-12'-(cyclobutylmethyl)-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	821.2
40	 MeI  (Aurum)	2, 5, 8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-12'-(cyclobutylmethyl)-7'-methoxy-11'-methyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	819.2
41	 MeI  (Aurum)	2, 5, 8		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-12'-(cyclobutylmethyl)-7'-methoxy-11'-methyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	819.2

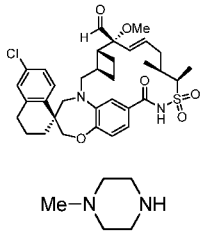
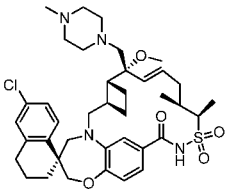
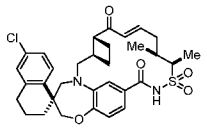
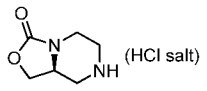
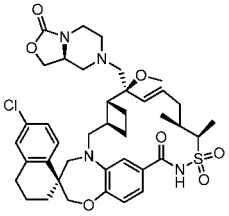
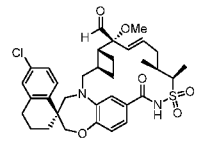
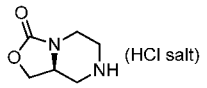
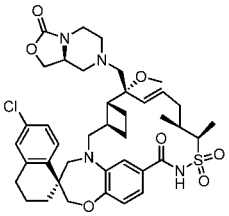
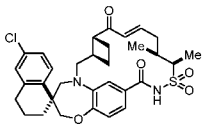
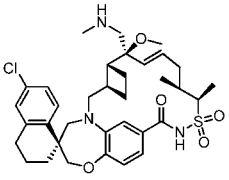
42	 EtI  (Aurum)	1 (R^1 = H), 5, 8		(1S,3'R,6'R,7'R,8'E,12'R)-6-chloro-7'-ethoxy-12'-ethyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	779.2
43	 EtI  (Aurum)	1 (R^1 = H), 5, 8		(1S,3'R,6'R,7'S,8'E,12'R)-6-chloro-7'-ethoxy-12'-ethyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	779.2
44	 EtI  (Pharmablock)	2, 5, 8		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-12'-(cyclobutylmethyl)-7'-ethoxy-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	835.2
45		2, 5, 8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-12'-(cyclobutylmethyl)-7'-ethoxy-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-	835.2

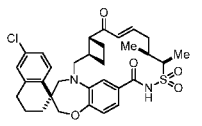
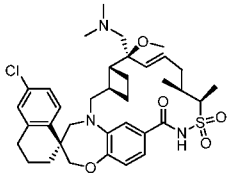
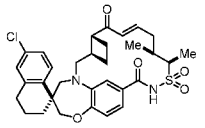
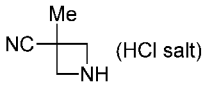
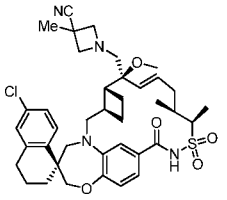
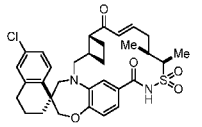
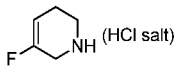
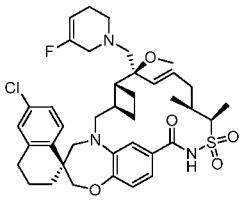
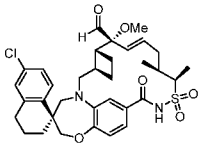
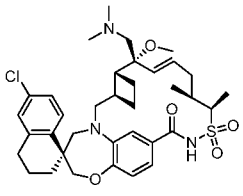
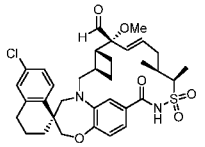
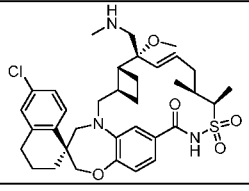
	EtI  (Pharmablock)			[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
46	 $B(Oallyl)_3$  (Pharmablock)	3, 8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-11',12'-dimethyl-7'-(2-propen-1-yloxy)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	793.2
47	 $B(OiPr)_3$  (Pharmablock)	3, 8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-11',12'-dimethyl-7'-(1-methylethoxy)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	795.2
48	 $B(On\text{-}Bu)_3$  (Pharmablock)	3, 8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-7'-butoxy-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	809.2
49	 $B(OCH_2CF_3)_3$	3, 8		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-11',12'-dimethyl-7'-(2,2,2-trifluoroethoxy)-3,4-	835.2

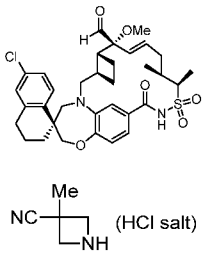
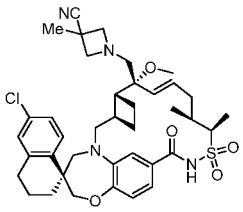
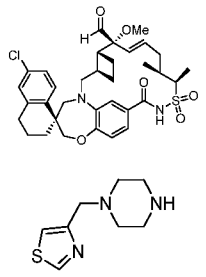
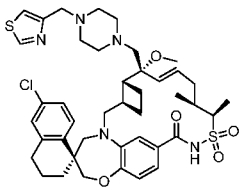
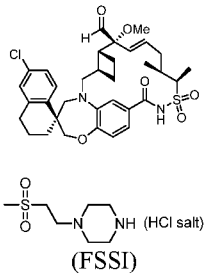
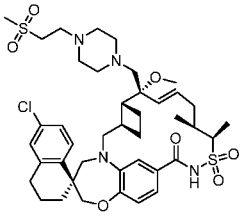
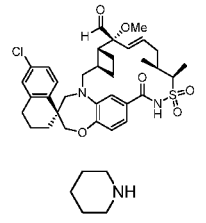
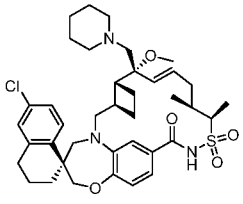
	 (Pharmablock)			dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
50	 $B(OCH_2CF_3)_3$  (Pharmablock)	3, 8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-11',12'-dimethyl-7'-(2,2,2-trifluoroethoxy)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	835.2
51	 $B(OiPr)_3$ 	3, 10		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-7'-(1-methylethoxy)-7'-(((3R)-3-methyl-4-(1-methylethyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	795.2
52	 MeI 	5, 12		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(4-morpholinylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	712.2
53	 	12		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(4-morpholinylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,	712.3

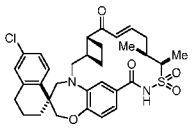
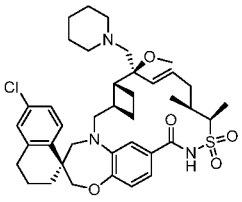
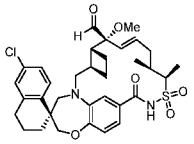
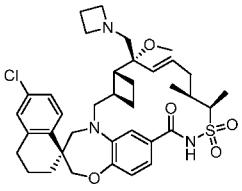
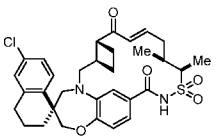
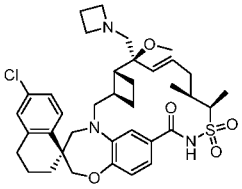
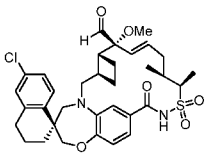
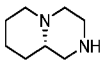
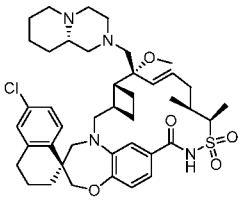
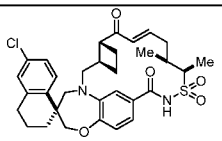
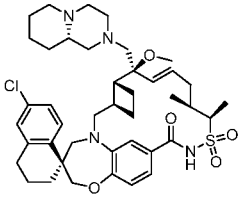
				24]tetraen]-15'-one 13',13'-dioxide	
54	 (Enamine)	12		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-7'-((4-(2-methoxyethyl)-3-oxo-1-piperazinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	783.2
55	 MeI  (Enamine)	5, 12		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-7'-((4-(2-methoxyethyl)-3-oxo-1-piperazinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	783.2
56	 MeI  (Synthonix)	5, 10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	767.3
57	 MeI  (Synthonix)	5, 10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((9aR)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	767.3

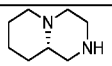
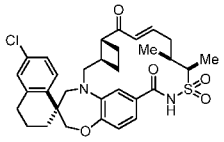
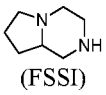
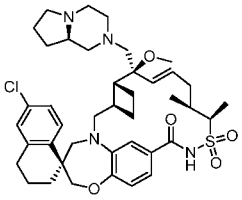
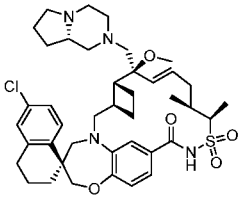
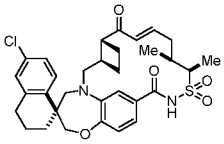
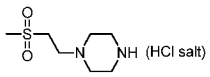
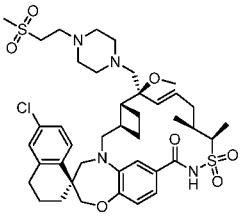
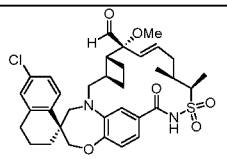
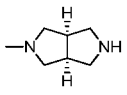
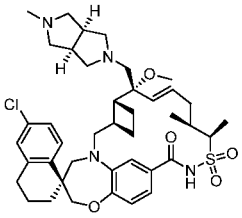
58	  (HCl salt) (Synthonix)	10		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((9aR)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	767.3
59	 MeI  (Matrix)	5, 10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((3-(dimethylamino)-3-methyl-1-azetidinyl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	739.4
60	  (Matrix)	10		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((3-(dimethylamino)-3-methyl-1-azetidinyl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	739.3
61	 	10		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-7'-((4-(2-methoxyethyl)-1-piperazinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	769.4

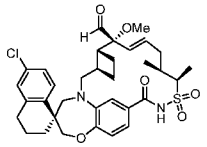
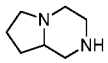
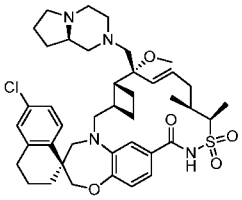
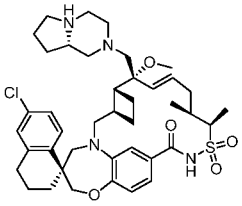
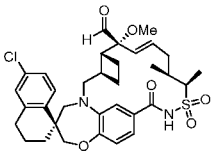
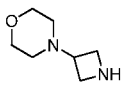
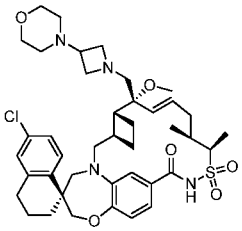
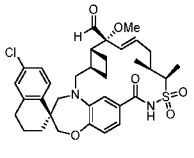
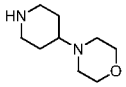
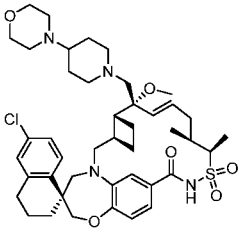
62		12		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-methyl-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	725.5
63	 MeI  (Ark Pharm)	5, 10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((8aS)-3-oxotetrahydro[1,3]oxazolo[3,4-a]pyrazin-7(1H)-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	767.3
64	  (Ark Pharm)	10		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((8aS)-3-oxotetrahydro[1,3]oxazolo[3,4-a]pyrazin-7(1H)-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	767.3
65	 MeI $MeNH_2 \cdot HCl$	5, 10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((methylamino)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	656.4

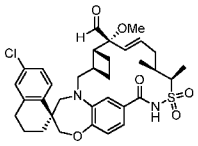
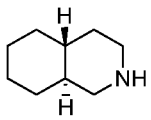
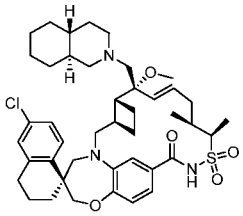
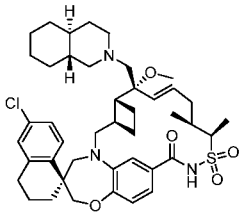
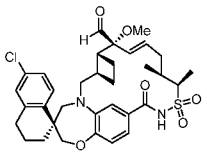
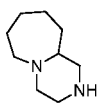
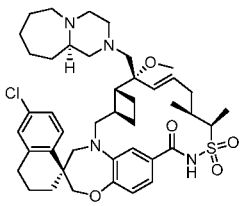
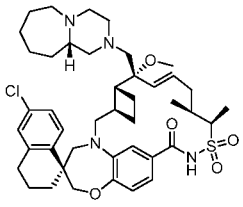
66	 MeI $Me_2NH \cdot HCl$	5, 10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((dimethylamino)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	670.3
67	 MeI  (FSSI)	5, 10		1-(((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)methyl)-3-methyl-3-azetidinecarbonitrile	721.3
68	 MeI  (FSSI)	5, 10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((5-fluoro-3,6-dihydro-1(2H)-pyridinyl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	726.3
69	 $Me_2NH \cdot HCl$	10		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((dimethylamino)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	670.2
70		10		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((methylamino)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-	656.2

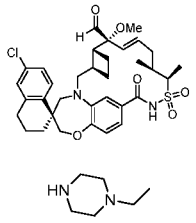
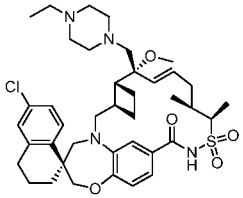
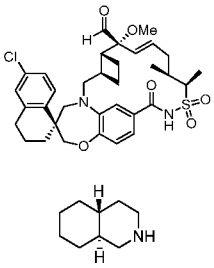
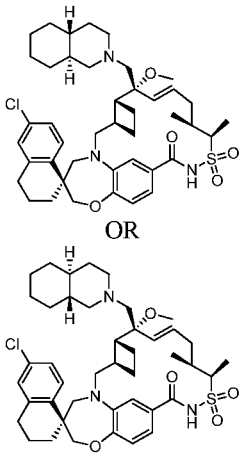
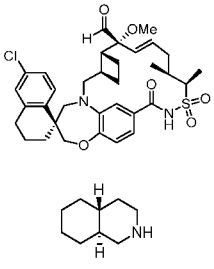
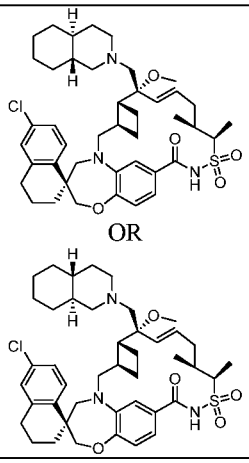
	$MeNH_2 \cdot HCl$			[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
71	 (FSSI)	10		1-(((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)methyl)-3-methyl-3-azetidinecarbonitrile	721.3
72	 (FSSI)	10		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-(1,3-thiazol-4-ylmethyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	808.2
73	 (FSSI)	10		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-(2-(methylsulfonyl)ethyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	817.2
74		10		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(1-piperidinylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	710.3

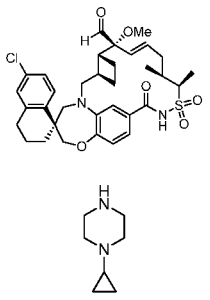
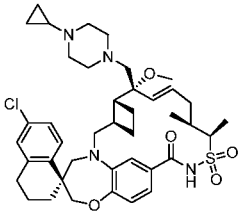
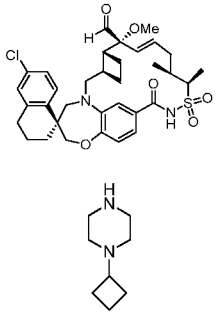
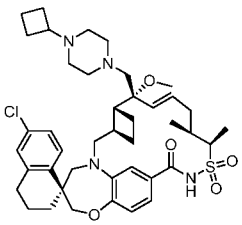
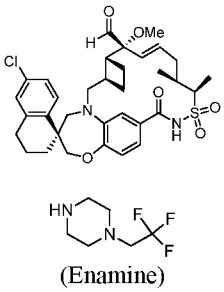
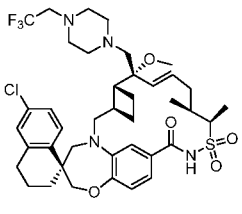
75	 MeI	5, 10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(1-piperidinylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	710.2
76		10		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-7'-(1-azetidinylmethyl)-6-chloro-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	682.3
77	 MeI	5, 10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-7'-(1-azetidinylmethyl)-6-chloro-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	682.3
78	  (J&W PharmLab)	10		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((9aS)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	765.8
79	 MeI	5, 10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((9aS)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-	765.8

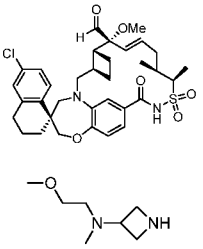
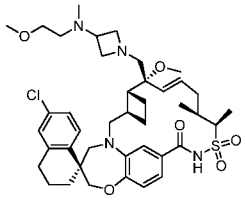
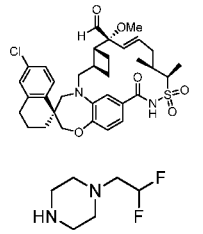
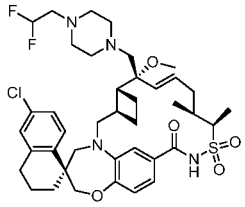
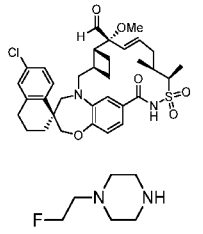
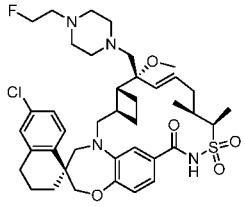
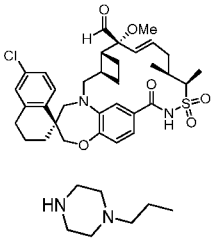
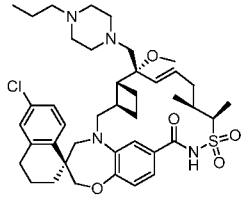
	 (J&W PharmLab)			spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
80	 MeI  (FSSI)	5, 10	 AND 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((8aR)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-ylmethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((8aS)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-ylmethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	751.8
81	 MeI  (Enamine)	5, 9		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-(2-(methylsulfonyl)ethyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	818.0
82	  (Enamine)	8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazat	751.2

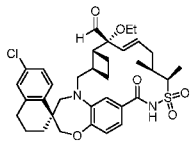
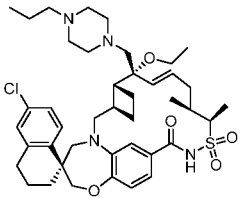
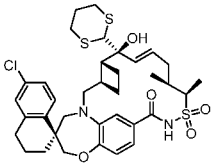
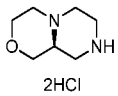
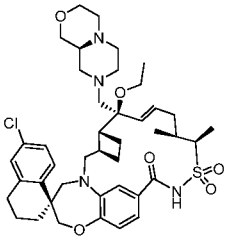
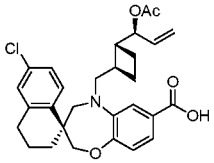
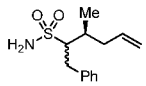
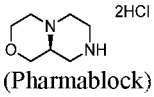
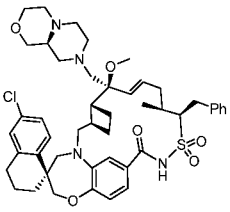
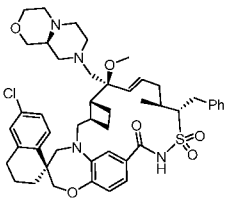
				etracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
83	  (Enamine)	9	 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((8aR)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-ylmethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide|(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((8aS)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-ylmethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	751.2
84	  (HCl salt) (ChemBridge Corp.)	9		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((3-(4-morpholinyl)-1-azetidinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	767.2
85	  (Oakwood)	8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-(4-morpholinyl)-1-piperidinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	795.9

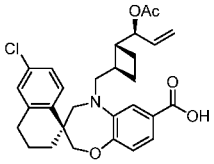
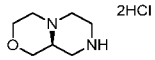
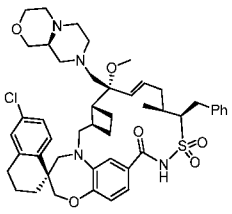
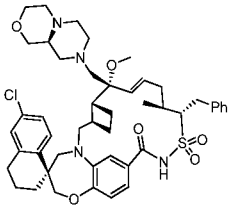
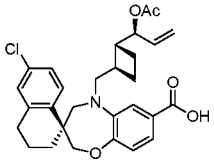
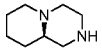
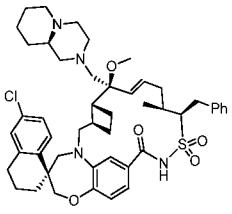
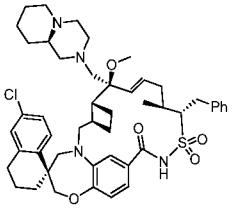
86	 	8	 AND 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4aR,8aS)-octahydro-2(1H)-isoquinolinylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4aS,8aR)-octahydro-2(1H)-isoquinolinylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	764.8
87	  (Oakwood)	8	 AND 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((10aR)-octahydropyrazino[1,2-a]azepin-2(1H)-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((10aS)-octahydropyrazino[1,2-a]azepin-2(1H)-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	779.8

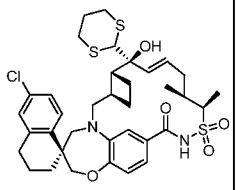
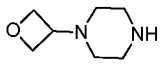
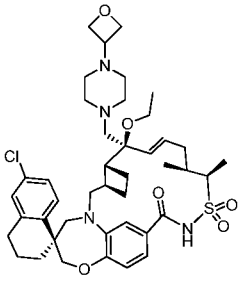
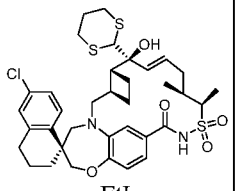
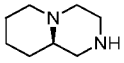
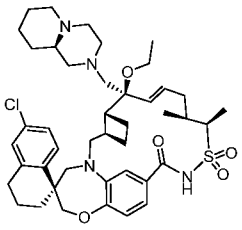
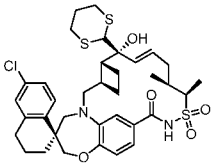
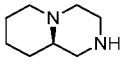
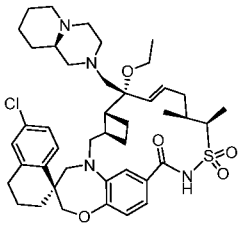
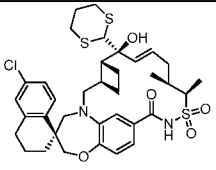
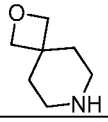
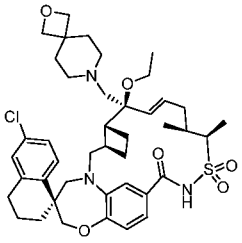
88		8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((4-ethyl-1-piperazinyl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	739.8
89		8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4aR,8aS)-octahydro-2(1H)-isoquinolinylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4aS,8aR)-octahydro-2(1H)-isoquinolinylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	764.2
90		8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4aS,8aR)-octahydro-2(1H)-isoquinolinylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR	764.2

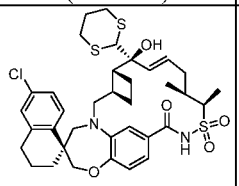
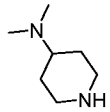
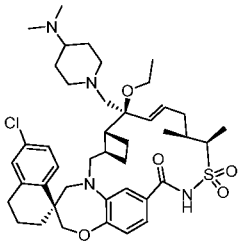
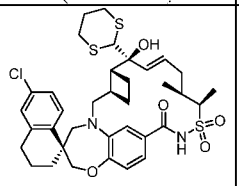
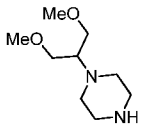
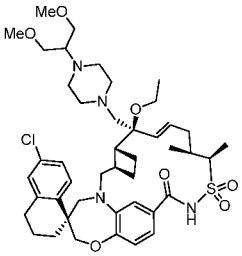
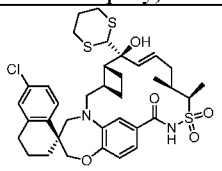
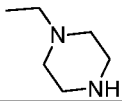
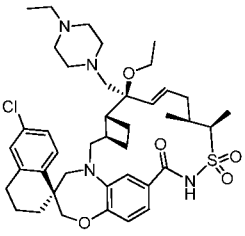
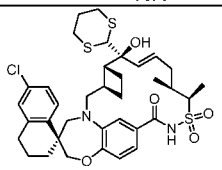
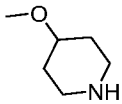
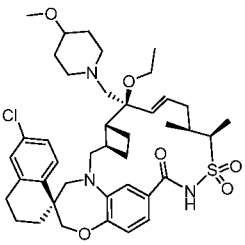
				(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4aR,8aS)-octahydro-2(1H)-isoquinolinylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
91	 (Combi-Blocks)	8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((4-cyclopropyl-1-piperazinyl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	751.8
92	 (Asta Tech)	8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((4-cyclobutyl-1-piperazinyl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	765.8
93	 (Enamine)	8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-(2,2,2-trifluoroethyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	794.0

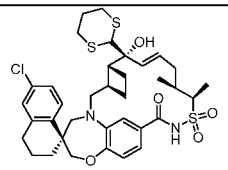
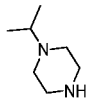
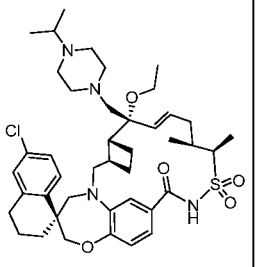
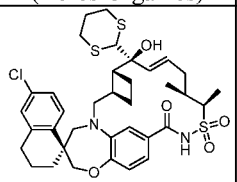
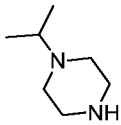
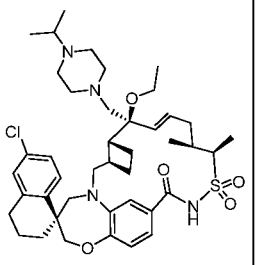
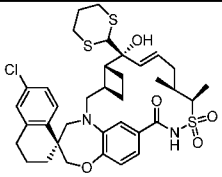
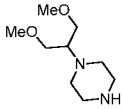
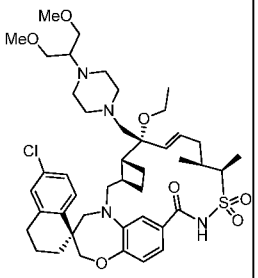
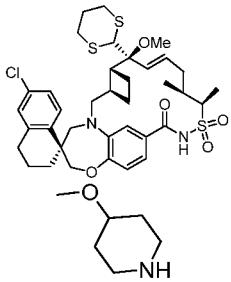
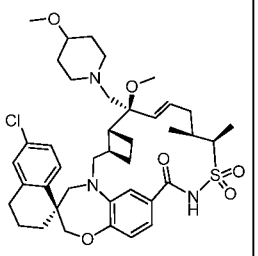
94	 (HCl salt) (Ryan Scientific)	9		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-7'-((3-((2-methoxyethyl)(methyl)amino)-1-azetidinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	769.8
95	 (Enamine)	8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((4-(2,2-difluoroethyl)-1-piperazinyl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	775.8
96	 (HCl salt) (Ark Pharm)	9		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((4-(2-fluoroethyl)-1-piperazinyl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	757.2
97	 (Enamine)	8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-propyl-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	753.3

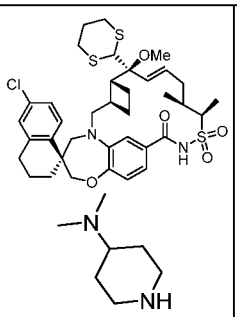
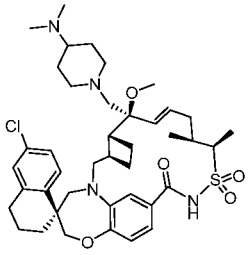
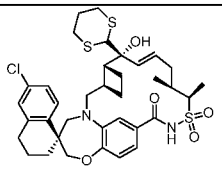
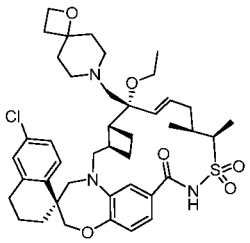
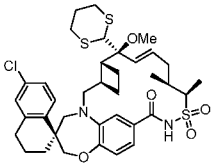
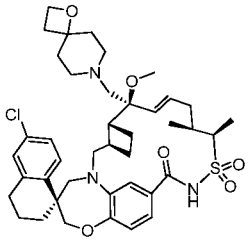
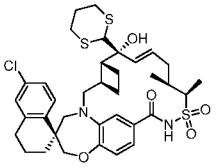
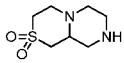
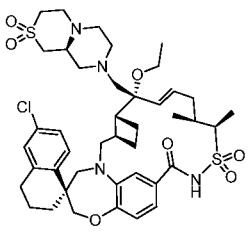
98	 (Enamine)	8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-11',12'-dimethyl-7'-((4-propyl-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	767.3
101	 EtI  2HCl (Pharmablock)	5, 9		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-ethoxy-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	781.8
102	  MeI  2HCl (Pharmablock)	1, 5, 9	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-12'-benzyl-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'S)-12'-benzyl-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	844.0

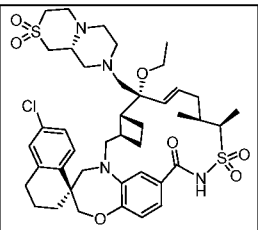
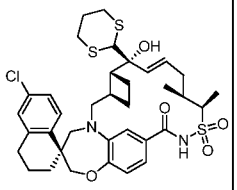
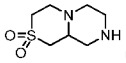
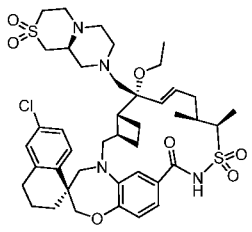
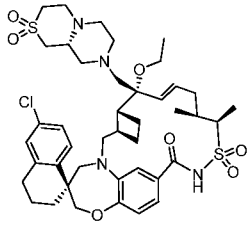
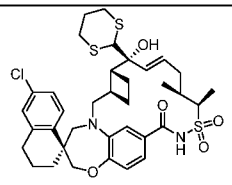
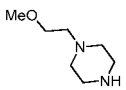
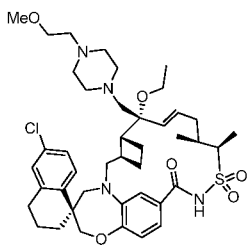
103	 MeI  (Pharmablock)	1, 5, 9	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-12'-benzyl-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'S)-12'-benzyl-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	844.0
104	 MeI  (J&W Pharmlab)	1, 5, 8	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-12'-benzyl-6-chloro-7'-methoxy-11'-methyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'S)-12'-benzyl-6-chloro-7'-methoxy-11'-methyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,	841.2

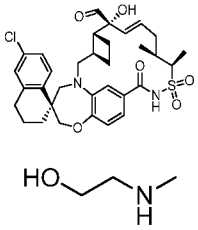
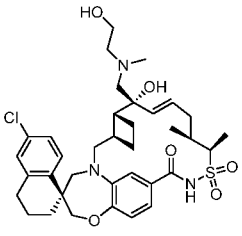
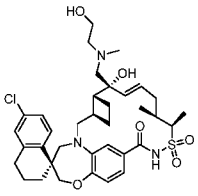
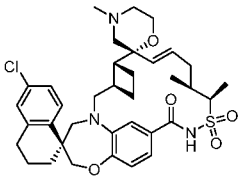
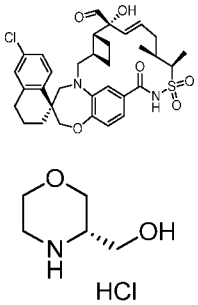
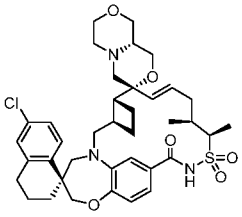
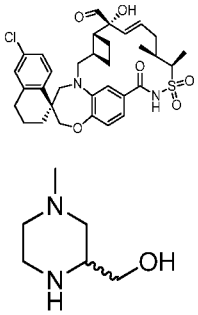
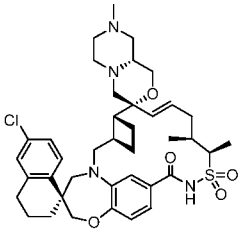
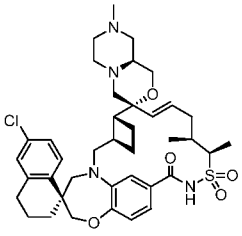
				24]tetraen]-15'-one 13',13'-dioxide	
106	 EtI  (Astatech)	5, 8		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-ethoxy-11',12'-dimethyl-7'-((4-(3-oxetanyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	781.2
107	 EtI  (Aurum Pharmtech)	5, 8		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-ethoxy-11',12'-dimethyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	779.3
108	 EtI  (Aurum Pharmtech)	5, 8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-11',12'-dimethyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	779.3
109	 EtI 	5, 8		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-ethoxy-11',12'-dimethyl-7'-(2-oxa-7-azaspiro[3.5]non-7-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	766.3

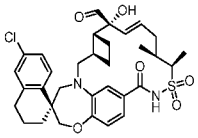
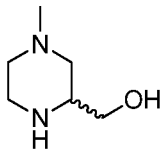
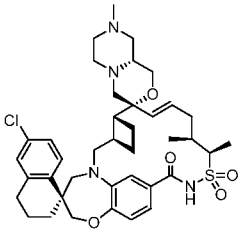
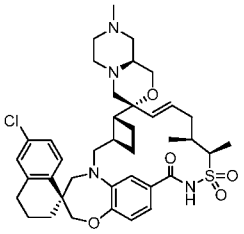
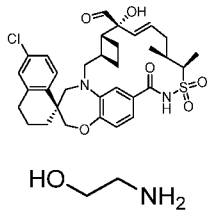
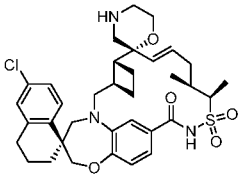
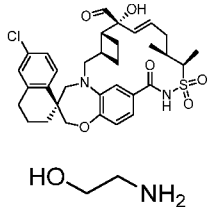
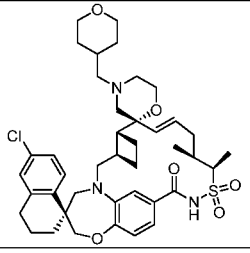
	(Astatech)				
110	 EtI  (Oakwood)	5, 8		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((4-(dimethylamino)-1-piperidinyl)methyl)-7'-ethoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	767.3
111	 EtI  (FCH Group Company)	5, 8		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-ethoxy-7'-((4-(2-methoxy-1-(methoxymethyl)ethyl)-1-piperazinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	827.2
112	 EtI 	5, 8		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-ethoxy-7'-((4-ethyl-1-piperazinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	753.3
113	 EtI  (Combi-Blocks)	5, 8		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-ethoxy-7'-((4-methoxy-1-piperidinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	754.8

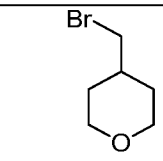
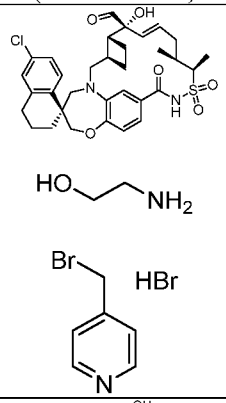
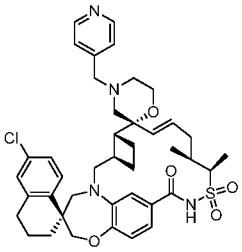
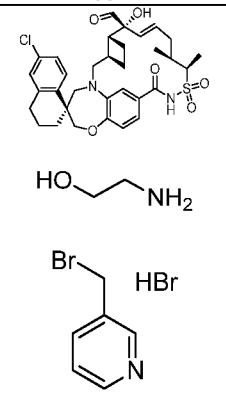
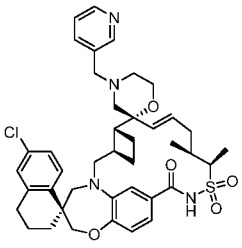
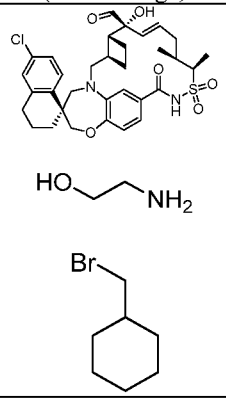
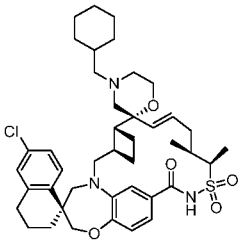
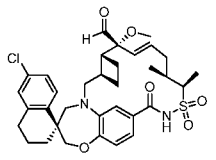
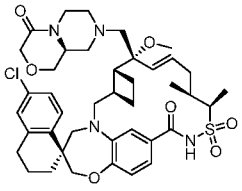
114	 EtI  (Acros Organics)	5, 8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-11',12'-dimethyl-7'-((4-(1-methylethyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	767.3
115	 EtI  (Acros Organics)	5, 8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-11',12'-dimethyl-7'-((4-(1-methylethyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	767.8
116	 EtI  (FCH Group)	5, 8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-7'-((4-(2-methoxy-1-(methoxymethyl)ethyl)-1-piperazinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	828.0
117	 (Combi-Blocks)	5, 8		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-7'-((4-methoxy-1-piperidinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	740.7

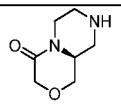
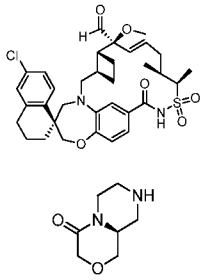
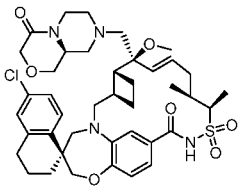
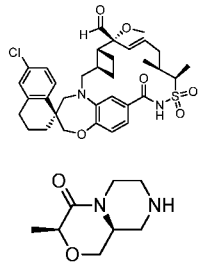
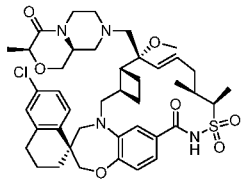
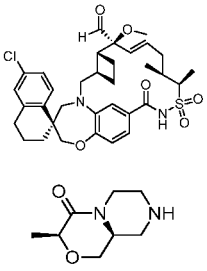
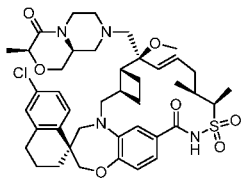
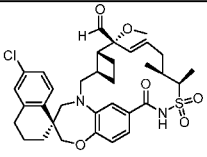
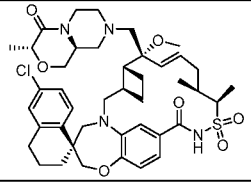
118	 (Oakwood)	5, 8		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((4-(dimethylamino)-1-piperidinyl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	753.7
119	 EtI (Frontier Scientific)	5, 8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-11',12'-dimethyl-7'-(1-oxa-7-azaspiro[3.5]non-7-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	766.8
120	 (Oakwood)	5, 8		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(1-oxa-7-azaspiro[3.5]non-7-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	752.8
121	 EtI  (after freebase the bis-HCl salt; FCH kGroup)	5, 8	 OR	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(((9aS)-2,2-dioxidohexahydropyrazino[2,1-c][1,4]thiazin-8(1H)-yl)methyl)-7'-ethoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR 1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(((9aR)-2,2-dioxidohexahydropyrazino[	830.0

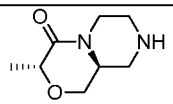
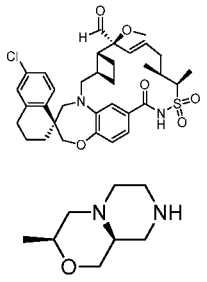
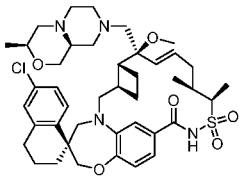
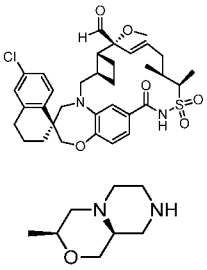
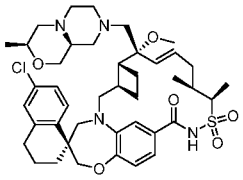
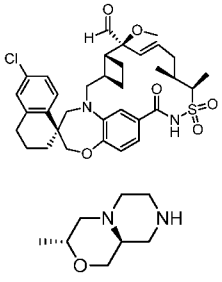
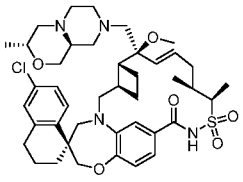
				2,1-c][1,4]thiazin-8(1H)-yl)methyl)-7'-ethoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
122	 EtI  (after freebase of bis-HCl salt; FCH Group)	5,8	 OR 	1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(((9aS)-2,2-dioxidohexahydropyrazino[2,1-c][1,4]thiazin-8(1H)-yl)methyl)-7'-ethoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR 1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(((9aR)-2,2-dioxidohexahydropyrazino[2,1-c][1,4]thiazin-8(1H)-yl)methyl)-7'-ethoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	830.0
123	 EtI  (Combi-blocks)	5,8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethoxy-7'-((4-(2-methoxyethyl)-1-piperazinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	783.9

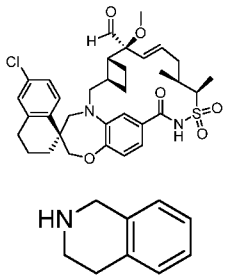
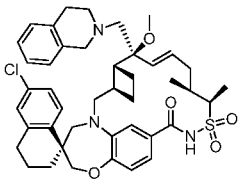
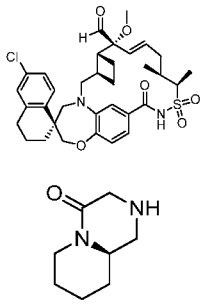
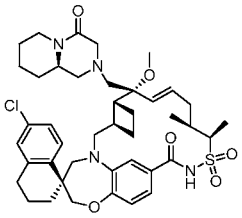
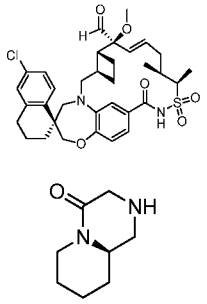
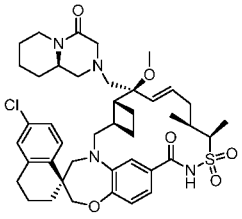
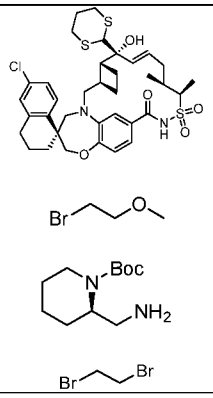
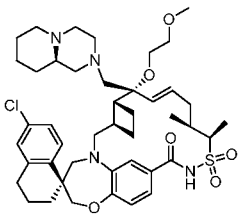
129	 (TCI)	See Example 138 (Step 1)		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(((2-hydroxyethyl)(methyl)amino)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	686.3
130		See Example 138 (Step 2)		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-4'',11',12'-trimethyl-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-7',2''-[1,4]oxazinan]-15'-one 13',13'-dioxide	668.3
131	 HCl (Tyger Sci.)	See Example 138 (Step 1 with Net_3 due to HCl salt, Step 2)		(1S,3'R,6'R,7'R,8'E,9a''R,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4,6'',7'',9'',9a''-hexahydro-1''H,2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-7',3''-[1,4]oxazino[3,4-c][1,4]oxazin]-15'-one 13',13'-dioxide	710.2
132	 (ChemBridge)	See Example 138 (Steps 1-2)	 OR 	(1S,3'R,6'R,7'R,8'E,9a''R,11'S,12'R)-6-chloro-8'',11',12'-trimethyl-1'',3,4,6'',7'',8'',9'',9a''-octahydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-7',3''-pyrazino[2,1-c][1,4]oxazin]-15'-one 13',13'-dioxide Or (1S,3'R,6'R,7'R,8'E,9a''S,11'S,12'R)-6-chloro-8'',11',12'-trimethyl-1'',3,4,6'',7'',8'',9'',9a''-	723.3

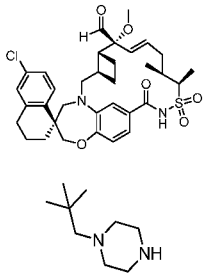
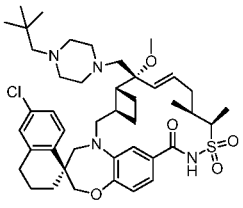
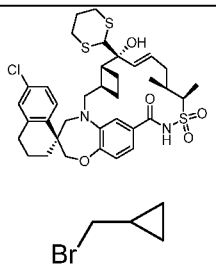
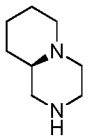
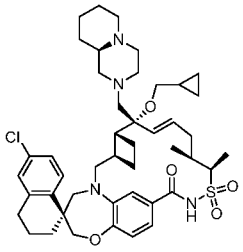
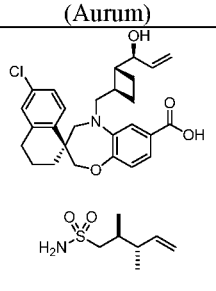
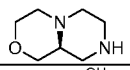
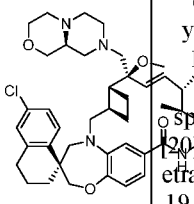
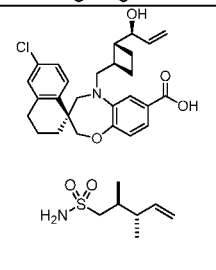
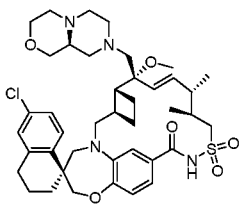
				octahydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-7',3''-pyrazino[2,1-c][1,4]oxazin]-15'-one 13',13'-dioxide	
133	  (ChemBridge)	See Example 138 (Steps 1-2)	 OR 	(1S,3'R,6'R,7'R,8'E,9a''R,11'S,12'R)-6-chloro-8'',11',12'-trimethyl-1'',3,4,6'',7'',8'',9'',9a''-octahydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-7',3''-pyrazino[2,1-c][1,4]oxazin]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,9a''S,11'S,12'R)-6-chloro-8'',11',12'-trimethyl-1'',3,4,6'',7'',8'',9'',9a''-octahydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-7',3''-pyrazino[2,1-c][1,4]oxazin]-15'-one 13',13'-dioxide	723.3
134		See Example 138 (Steps 1-2)		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-7',2''-[1,4]oxazinan]-15'-one 13',13'-dioxide	654.2
135		See Example 138 (Steps 1-3)		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-4''-(tetrahydro-2H-pyran-4-ylmethyl)-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~	752.3

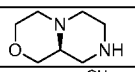
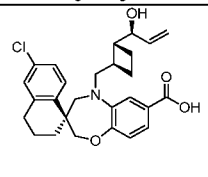
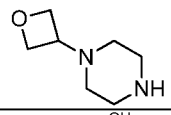
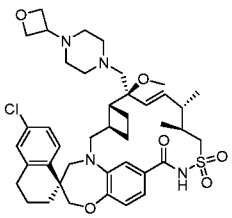
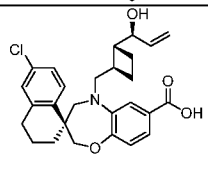
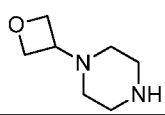
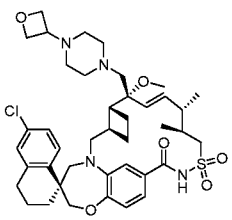
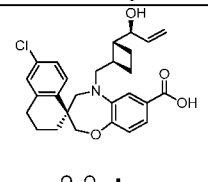
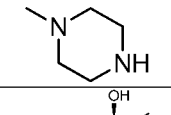
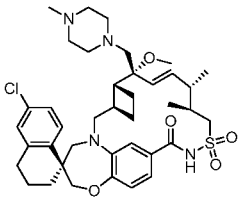
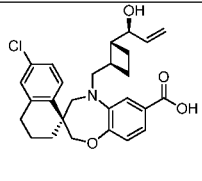
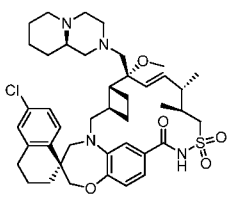
	 (Combi-Blocks)			19,24~]pentacosa[8,16,18,24]tetraene-7',2''-[1,4]oxazinan]-15'-one 13',13'-dioxide	
136		See Example 138 (Steps 1-3)		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-4''-(4-pyridinylmethyl)-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-7',2''-[1,4]oxazinan]-15'-one 13',13'-dioxide	745.3
137	 (ChemBridge)	See Example 138 (Steps 1-3)		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-4''-(3-pyridinylmethyl)-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-7',2''-[1,4]oxazinan]-15'-one 13',13'-dioxide	745.3
139		See Example 138 (Steps 1-3)		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-4''-(cyclohexylmethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-7',2''-[1,4]oxazinan]-15'-one 13',13'-dioxide	750.3
140		8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aS)-4-oxohexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methyl)-3,4-dihydro-	781.2

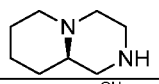
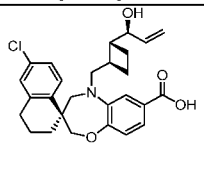
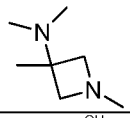
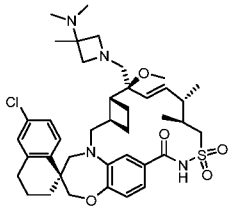
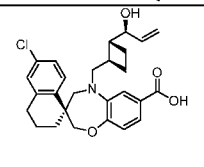
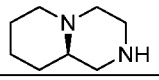
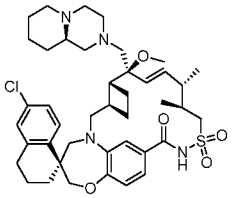
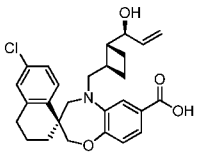
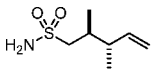
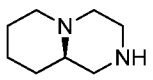
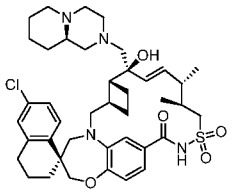
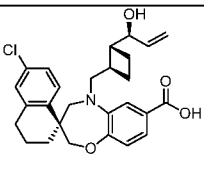
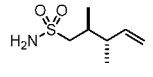
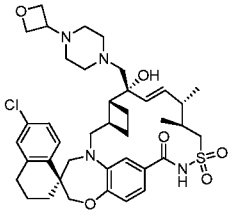
				2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
141		8		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aS)-4-oxohexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	781.2
142		8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((3S,9aS)-3-methyl-4-oxohexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	795.3
143		8		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((3S,9aS)-3-methyl-4-oxohexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	795.2
144		8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((3R,9aS)-3-methyl-4-oxohexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-	795.3

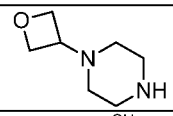
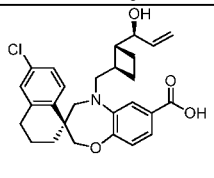
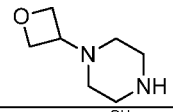
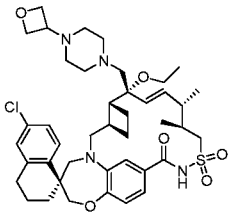
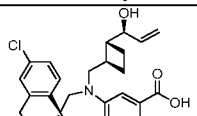
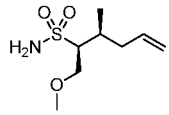
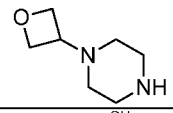
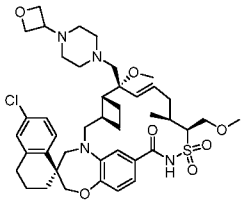
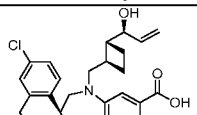
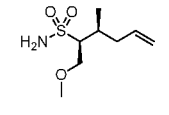
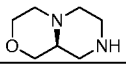
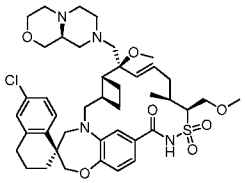
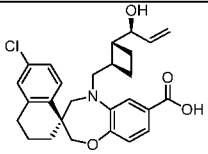
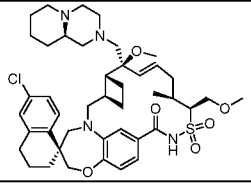
				yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
145		8		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((3S,9aS)-3-methylhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	781.4
146		8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((3S,9aS)-3-methylhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	781.2
147		8		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((3R,9aS)-3-methylhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	781.2

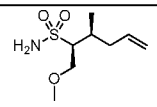
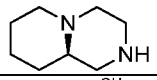
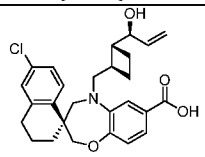
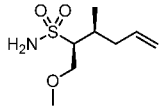
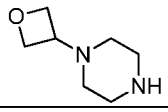
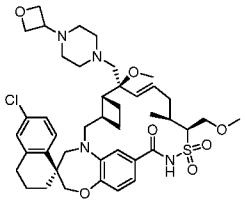
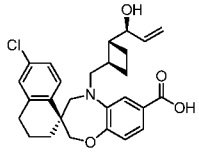
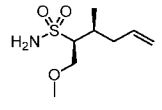
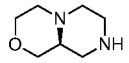
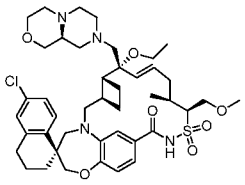
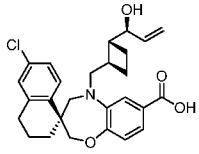
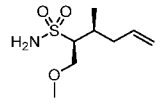
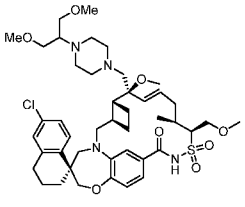
148	 (Frontier Scientific)	8		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(3,4-dihydro-2(1H)-isoquinolinylmethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	758.3
149		8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aR)-4-oxooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	779.3
150		8		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aR)-4-oxooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	779.3
152		See example 151		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(2-methoxyethoxy)-11',12'-dimethyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	809.2

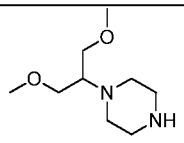
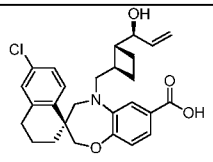
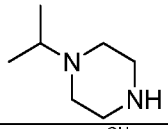
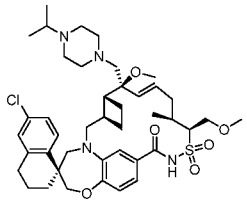
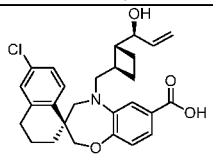
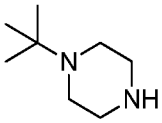
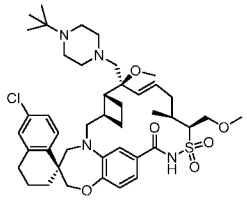
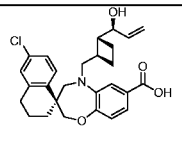
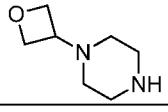
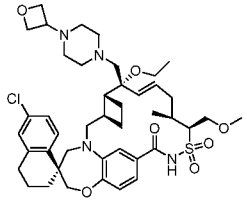
153		8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((4-(2,2-dimethylpropyl)-1-piperazinyl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	781.3
155	 (Chem-Impex)  (Aurum)	5, 8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(cyclopropylmethoxy)-11',12'-dimethyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	805.3
156	 MeI 	2, 5, 8		(1S,3'R,6'R,7'S,8'E,10'S,11'S)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-10',11'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	767
157	 MeI	2, 5, 8		(1S,3'R,6'R,7'R,8'E,10'S,11'S)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-10',11'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,	767.2

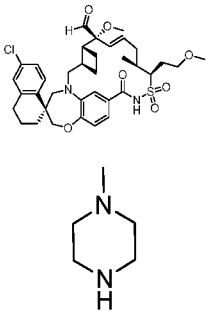
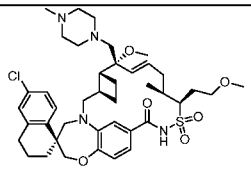
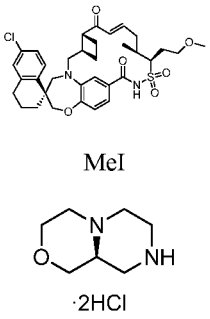
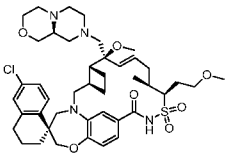
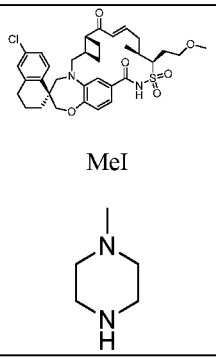
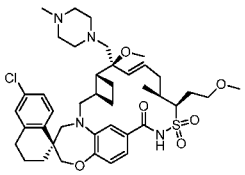
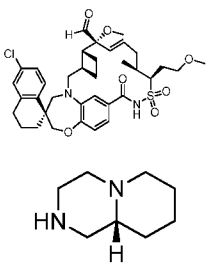
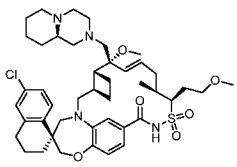
				24]tetraen]-15'-one 13',13'-dioxide	
158	 MeI 	2, 5, 8		(1S,3'R,6'R,7'S,8'E,10'S,11'S)-6-chloro-7'-methoxy-10',11'-dimethyl-7'-((4-(3-oxetanyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	767.2
159	 MeI 	2, 5, 8		(1S,3'R,6'R,7'R,8'E,10'S,11'S)-6-chloro-7'-methoxy-10',11'-dimethyl-7'-((4-(3-oxetanyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	767.2
160	 MeI 	2, 5, 8		(1S,3'R,6'R,7'R,8'E,10'S,11'S)-6-chloro-7'-methoxy-10',11'-dimethyl-7'-((4-methyl-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	725.2
161		2, 5, 8		(1S,3'R,6'R,7'R,8'E,10'S,11'S)-6-chloro-7'-methoxy-10',11'-dimethyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazat	765.2

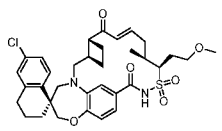
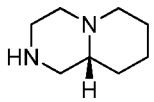
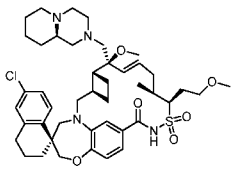
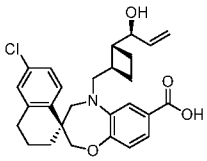
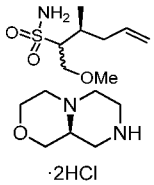
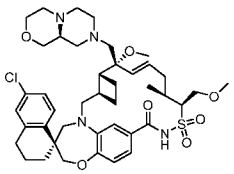
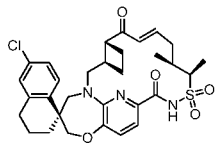
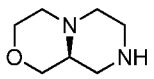
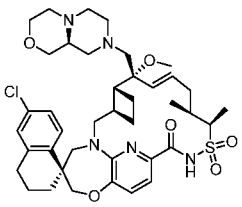
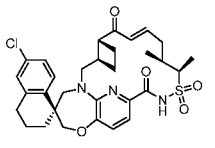
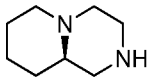
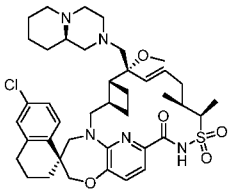
	MeI 			etracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
162	 MeI 	2, 5, 8		(1S,3'R,6'R,7'S,8'E,10'S,11'S)-6-chloro-7'-((3-(dimethylamino)-3-methyl-1-azetidinyl)methyl)-7'-methoxy-10',11'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	739.2
163	 MeI 	2, 5, 8		(1S,3'R,6'R,7'S,8'E,10'S,11'S)-6-chloro-7'-methoxy-10',11'-dimethyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	765.2
164	  	2, 5 (Step 1), 8		(1S,3'R,6'R,7'S,8'E,10'S,11'S)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-hydroxy-10',11'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	753.2
165	 	2 (Step 1), 5, 8		(1S,3'R,6'R,7'R,8'E,10'S,11'S)-6-chloro-7'-hydroxy-10',11'-dimethyl-7'-((4-(3-oxetanyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~	753.2

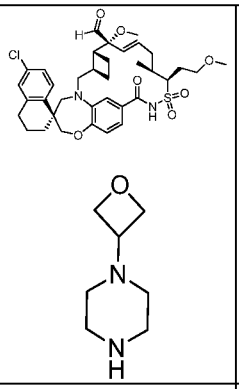
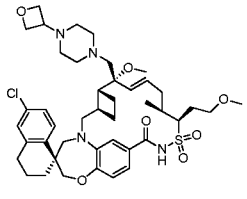
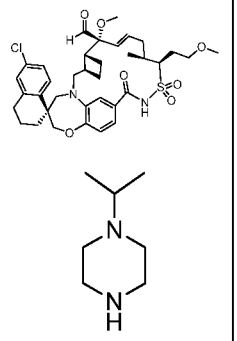
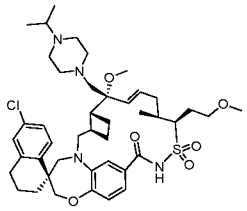
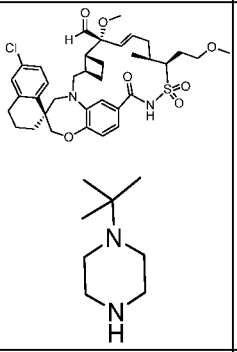
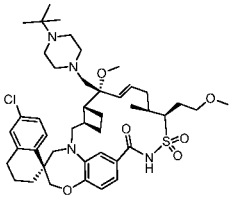
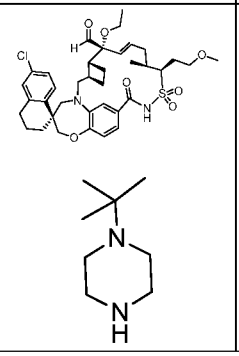
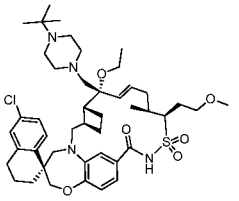
				19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
166	 EtI 	2, 5, 8		(1S,3'R,6'R,7'R,8'E,10'S,11'S)-6-chloro-7'-ethoxy-10',11'-dimethyl-7'-((4-(3-oxetanyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	781.2
167	  MeI 	2, 5, 8		(1S,3'R,6'R,7'R,8'E,11'S,12'S)-6-chloro-7'-methoxy-12'-(methoxymethyl)-11'-methyl-7'-((4-(3-oxetanyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	797.2
168	  MeI 	2, 5, 8		(1S,3'R,6'R,7'S,8'E,11'S,12'S)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-12'-(methoxymethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	797.2
169		2, 5, 8		(1S,3'R,6'R,7'R,8'E,11'S,12'S)-6-chloro-7'-methoxy-12'-(methoxymethyl)-11'-methyl-7'-((9aR)-octahydro-2H-pyrido[1,2-	795.2

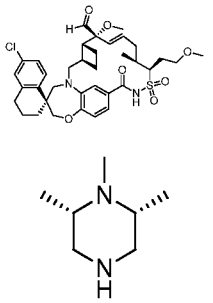
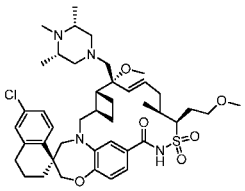
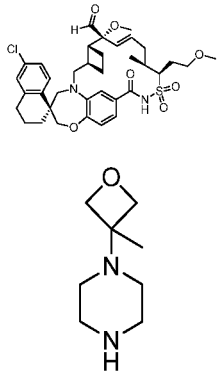
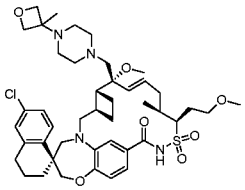
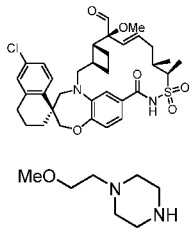
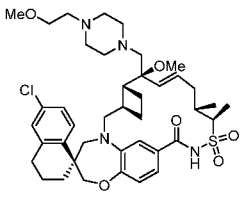
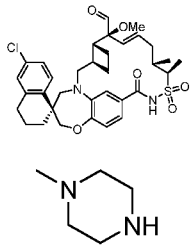
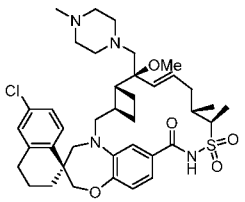
	 MeI 			a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
170	  MeI 	2, 5, 8		(1S,3'R,6'R,7'S,8'E,11'S,12'S)-6-chloro-7'-methoxy-12'-(methoxymethyl)-11'-methyl-7'-((4-(3-oxetanyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	797.2
171	  EtI 	2, 5, 8		(1S,3'R,6'R,7'R,8'E,11'S,12'S)-6-chloro-7'-ethoxy-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-12'-(methoxymethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	811.2
172	  MeI	2, 5, 8		(1S,3'R,6'R,7'S,8'E,11'S,12'S)-6-chloro-7'-methoxy-7'-((4-(2-methoxy-1-(methoxymethyl)ethyl)-1-piperazinyl)methyl)-12'-(methoxymethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	843.2

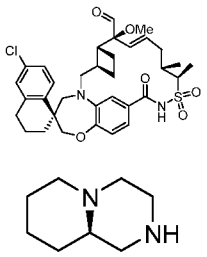
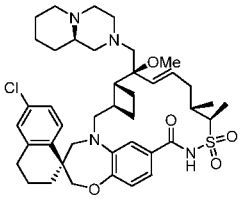
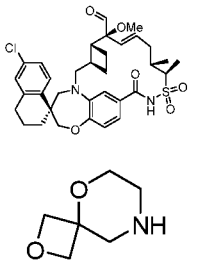
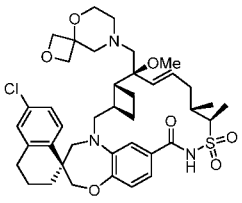
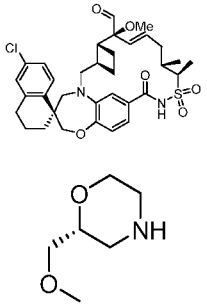
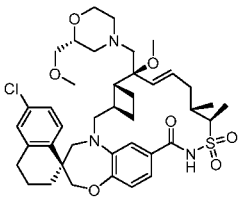
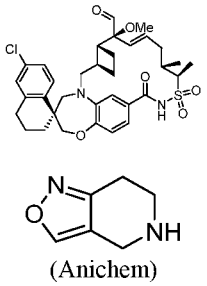
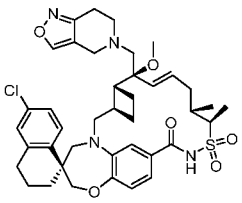
					
173	 MeI 	2, 5, 8		(1S,3'R,6'R,7'S,8'E,11'S,12'S)-6-chloro-7'-methoxy-12'-(methoxymethyl)-11'-methyl-7'-((4-(1-methylethyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	783.4
174	 MeI 	2, 5, 8		(1S,3'R,6'R,7'S,8'E,11'S,12'S)-7'-((4-tert-butyl-1-piperazinyl)methyl)-6-chloro-7'-methoxy-12'-(methoxymethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	797.2
175	 EtI 	2, 5, 8		(1S,3'R,6'R,7'R,8'E,11'S,12'S)-6-chloro-7'-ethoxy-12'-(methoxymethyl)-11'-methyl-7'-((4-(3-oxetanyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	811.2

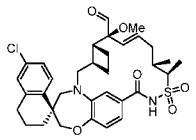
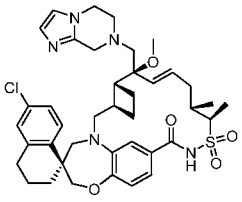
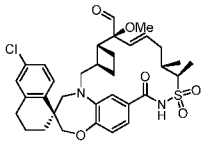
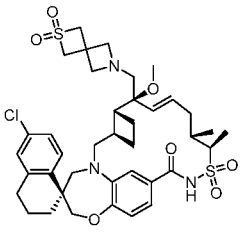
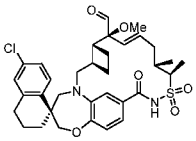
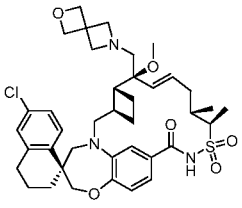
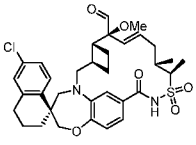
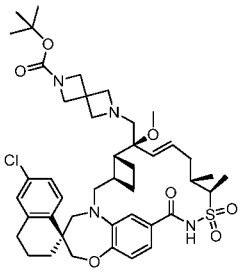
178		12		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-7'-((4-methyl-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	769.2
179		5, 10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	811.2
180		5, 12		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-7'-((4-methyl-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	769.2
181		12		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	809.0

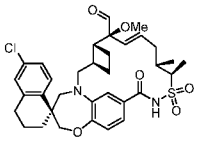
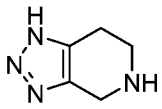
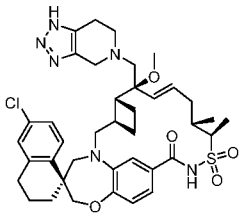
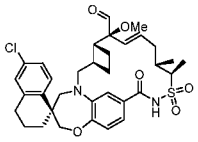
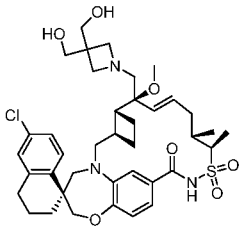
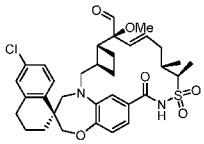
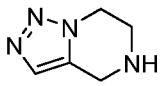
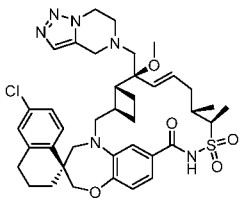
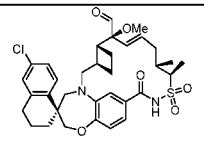
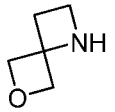
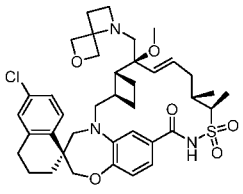
182	 MeI 	5, 12		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	809.2
184	  ·2HCl	1, 5, 11		(1S,3'R,6'R,7'R,8'E,11'S,12'S)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-12'-(methoxymethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	797.2
185	 MeI  ·2HCl	5, 11		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	768.2
186	 MeI 	5, 11		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	766.2

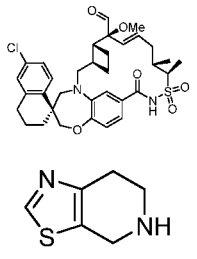
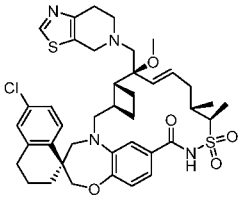
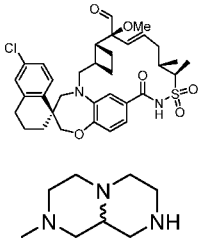
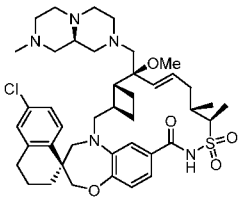
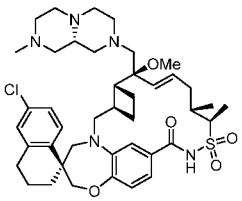
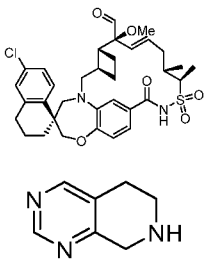
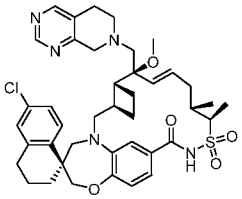
187		12		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-7'-((4-(3-oxetanyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	811.2
188		12		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-7'-((4-(1-methylethyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	797.2
189		12		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-7'-((4-tert-butyl-1-piperazinyl)methyl)-6-chloro-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	811.2
190		12		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-7'-((4-tert-butyl-1-piperazinyl)methyl)-6-chloro-7'-ethoxy-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	825.2

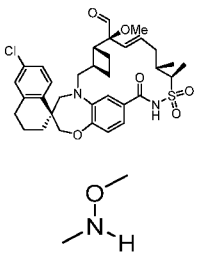
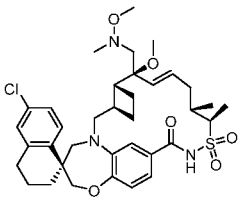
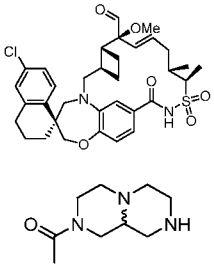
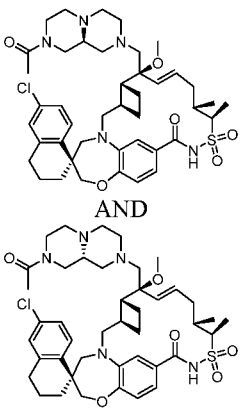
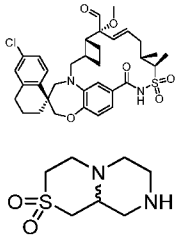
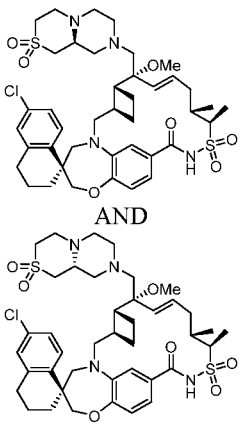
191		12		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-7'-(((3R,5S)-3,4,5-trimethyl-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	797.2
192		12		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-7'-((4-(3-methyl-3-oxetanyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	825.2
195		10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-7'-((4-(2-methoxyethyl)-1-piperazinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	769.2
196		10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-methyl-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	725.3

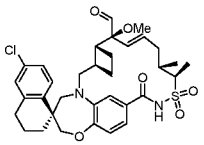
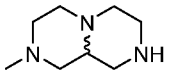
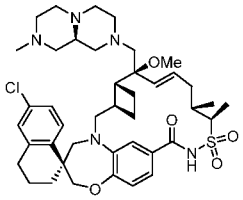
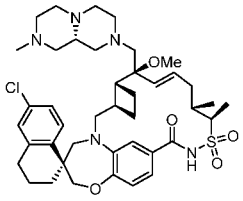
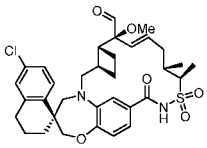
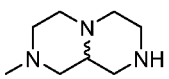
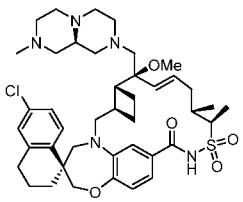
197	 (J&W PhamLab)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	765.3
198	 (A2Z Chemical)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2,5-dioxa-8-azaspiro[3.5]non-8-ylmethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	754.4
199	 (Ark Pharm, Inc.)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-7'-(((2R)-2-(methoxymethyl)-4-morpholinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	756.3
200	 (Anichem)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(6,7-dihydroisoxazolo[4,3-c]pyridin-5(4H)-ylmethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	749.3

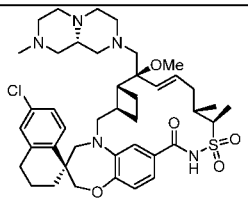
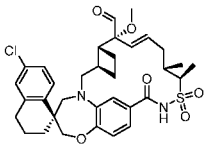
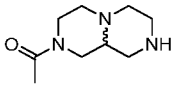
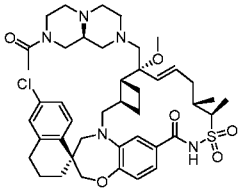
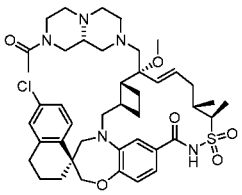
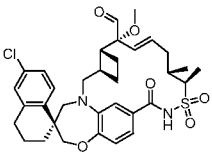
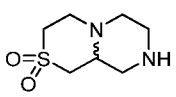
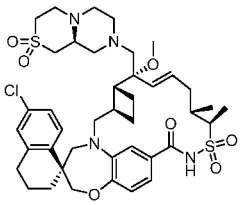
201	 (Anichem)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-ylmethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	748.2
202	 (Synthonix)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((2,2-dioxido-2-thia-6-azaspiro[3.3]hept-6-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	772.3
203	 (Advanced ChemTech)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-oxa-6-azaspiro[3.3]hept-6-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	724.3
204	 (Advanced ChemBlocks)	10		tert-butyl 6-(((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)methyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate	823.3

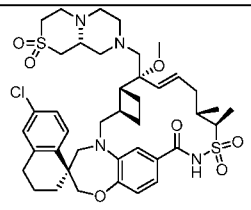
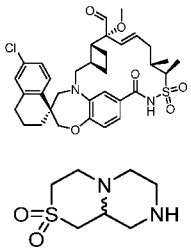
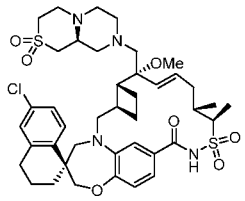
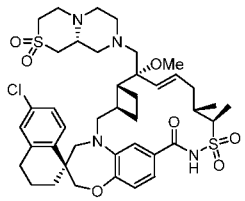
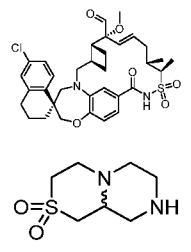
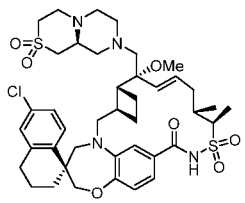
205	  (Enamine)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(1,4,6,7-tetrahydro-5H-[1,2,3]triazolo[4,5-c]pyridin-5-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	749.3
206	 (Advanced ChemTech)	10 (with in situ oxetane hydrolysis)		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-7'-((3,3-bis(hydroxymethyl)-1-azetidinyl)methyl)-6-chloro-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	742.3
207	  (Accela ChemBio, Inc.)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(6,7-dihydro[1,2,3]triazolo[1,5-a]pyrazin-5(4H)-ylmethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	749.5
208	  (Alfa Aesar, A Johnson-Matthey Company)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(6-oxa-1-azaspiro[3.3]hept-1-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	724.4

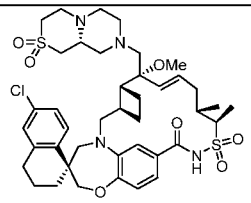
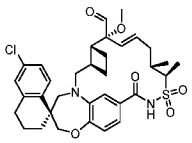
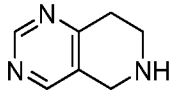
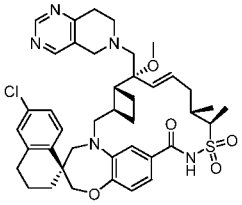
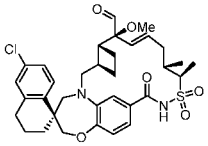
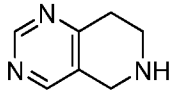
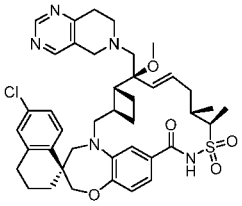
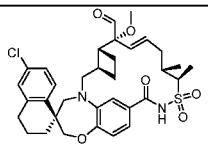
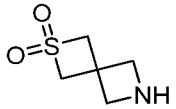
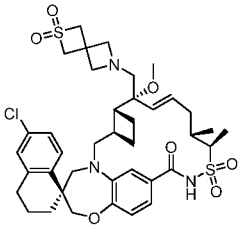
209		10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(6,7-dihydro[1,3]thiazolo[5,4-c]pyridin-5(4H)-ylmethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	765.5
210	 (ChemBridge)	10	 AND 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aR)-8-methyloctahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aS)-8-methyloctahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	780.5
211	 (Synthonix)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(5,8-dihydropyrido[3,4-d]pyrimidin-7(6H)-ylmethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	760.3

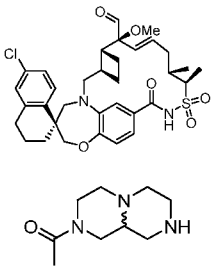
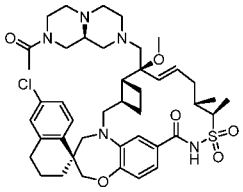
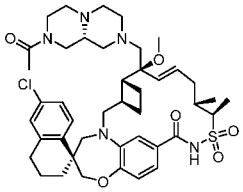
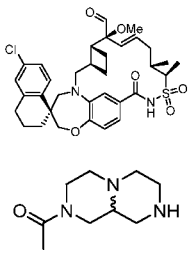
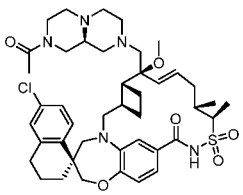
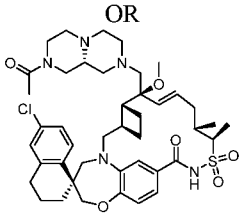
212		10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-7'-((methoxy(methyl)amino)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	686.5
214		10	 AND	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-7'-(((9aS)-8-acetyloctahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-6-chloro-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,8'E,11'S,12'R)-7'-(((9aR)-8-acetyloctahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-6-chloro-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	808.3
215	 (FCH1267684)	10	 AND	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(((9aS)-2,2-dioxidohexahydropyrazino[2,1-c][1,4]thiazin-8(1H)-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND	815.3

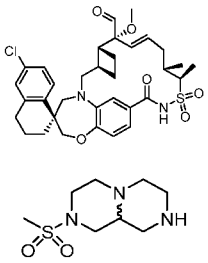
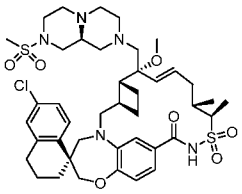
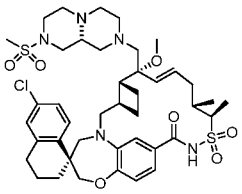
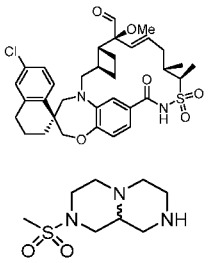
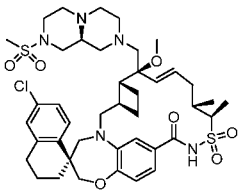
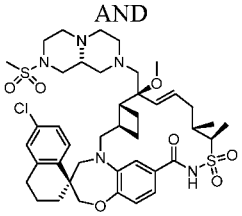
				(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(((9aR)-2,2-dioxidohexahydropyrazino[2,1-c][1,4]thiazin-8(1H)-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
216	  (ChemBridge)	10	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aR)-8-methyloctahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aS)-8-methyloctahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	780.5
217	  (ChemBridge)	10	 OR	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aR)-8-methyloctahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,	780.5

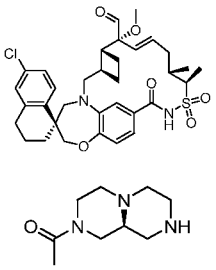
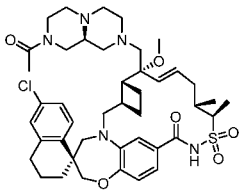
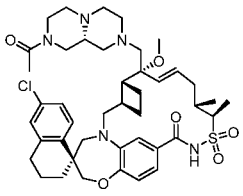
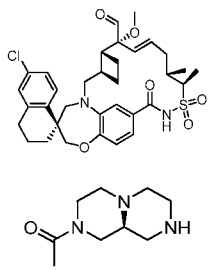
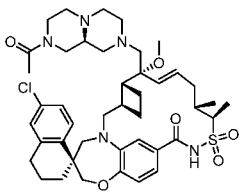
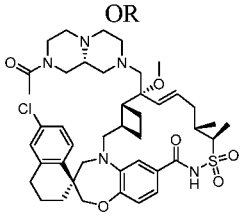
				24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aS)-8-methyloctahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
218	 	10	 AND 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-7'-(((9aR)-8-acetyloctahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-6-chloro-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'R,8'E,11'S,12'R)-7'-(((9aS)-8-acetyloctahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-6-chloro-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	808.3
219	 	10	 AND	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(((9aR)-2,2-dioxidohexahydropyrazino[2,1-c][1,4]thiazin-8(1H)-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,	815.2

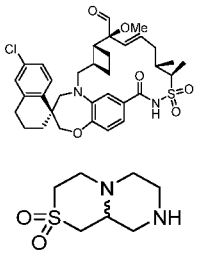
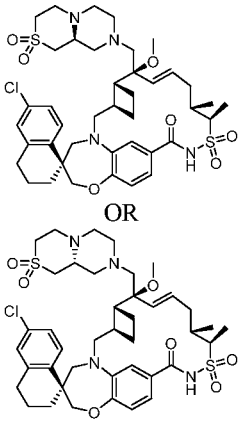
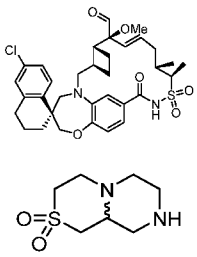
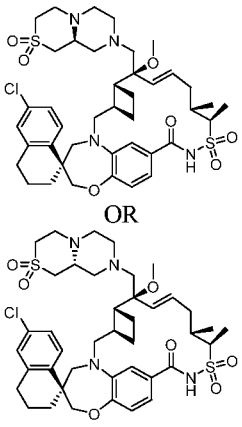
				24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(((9aS)-2,2-dioxidohexahydropyrazino[2,1-c][1,4]thiazin-8(1H)-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
220		10	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(((9aS)-2,2-dioxidohexahydropyrazino[2,1-c][1,4]thiazin-8(1H)-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(((9aR)-2,2-dioxidohexahydropyrazino[2,1-c][1,4]thiazin-8(1H)-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	815.2
221		10	 OR	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(((9aS)-2,2-dioxidohexahydropyrazino[2,1-c][1,4]thiazin-8(1H)-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazat	815.2

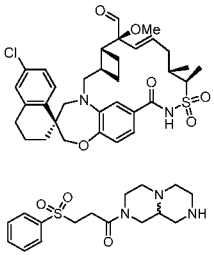
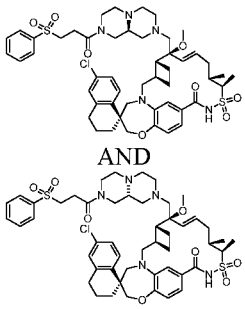
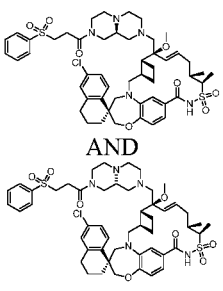
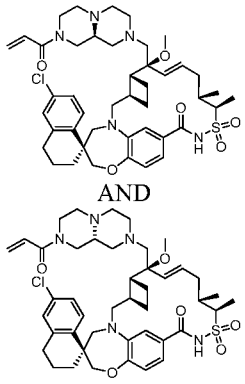
				etracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(((9aR)-2,2-dioxidohexahydropyrazino[2,1-c][1,4]thiazin-8(1H)-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
222	  (Ark Pharma)	8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-ylmethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	760.3
223	  (Ark Pharma)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-ylmethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	760.2
224	  (Synthonix)	10		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((2,2-dioxido-2-thia-6-azaspiro[3.3]hept-6-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~	772.0

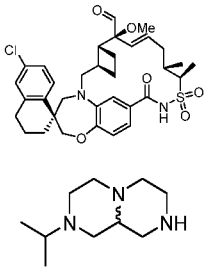
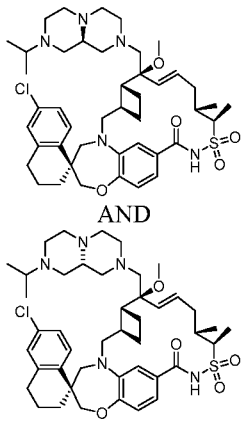
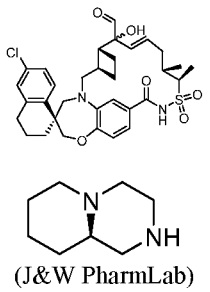
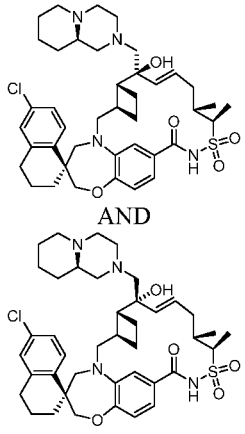
				19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
225		10	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-7'-(((9aS)-8-acetyloctahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-6-chloro-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-7'-(((9aR)-8-acetyloctahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-6-chloro-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	808.3
226		10	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-7'-(((9aS)-8-acetyloctahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-6-chloro-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-7'-(((9aR)-8-acetyloctahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-6-chloro-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,	808.3

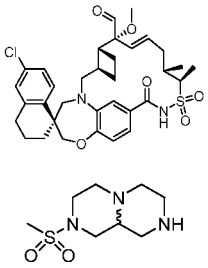
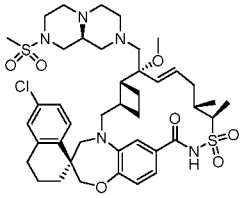
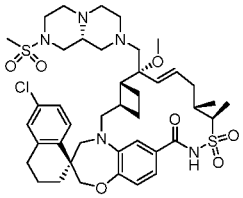
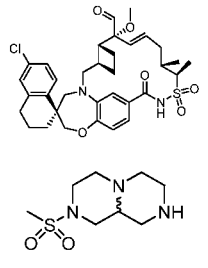
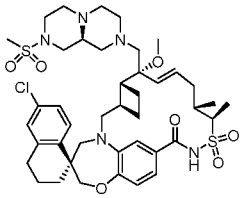
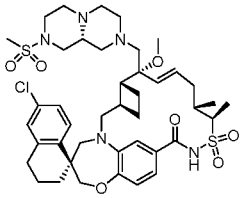
				24]tetraen]-15'-one 13',13'-dioxide	
227		10	 AND 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aR)-8-(methylsulfonyl)octahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aS)-8-(methylsulfonyl)octahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	844.3
228		10	 AND 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aR)-8-(methylsulfonyl)octahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aS)-8-(methylsulfonyl)octahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-	844.0

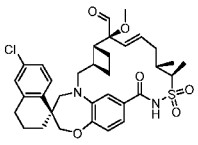
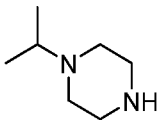
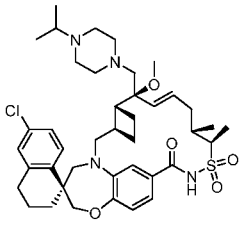
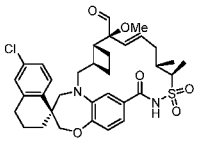
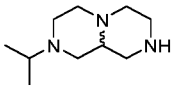
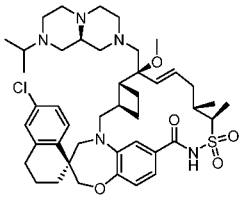
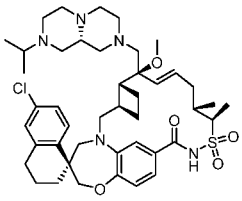
				[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
229		10	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-7'-(((9aS)-8-acetyloctahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-6-chloro-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-7'-(((9aR)-8-acetyloctahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-6-chloro-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	808.2
230		10	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-7'-(((9aS)-8-acetyloctahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-6-chloro-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-7'-(((9aR)-8-acetyloctahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-6-chloro-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazat	808.2

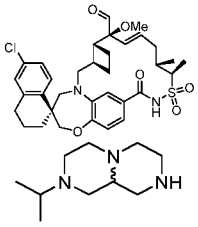
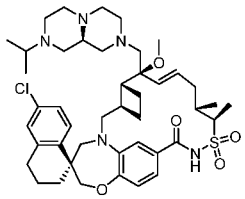
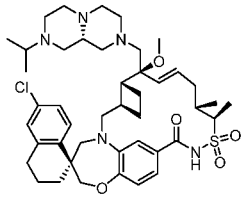
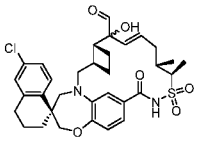
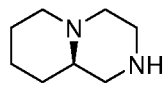
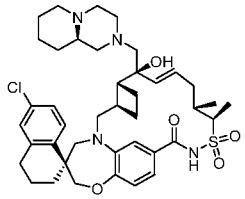
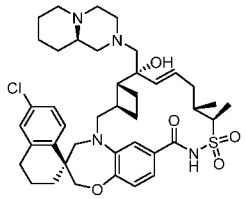
				etracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
231		10	 OR	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(((9aS)-2,2-dioxidohexahydropyrazino[2,1-c][1,4]thiazin-8(1H)-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(((9aR)-2,2-dioxidohexahydropyrazino[2,1-c][1,4]thiazin-8(1H)-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	815.1
232		10	 OR	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(((9aS)-2,2-dioxidohexahydropyrazino[2,1-c][1,4]thiazin-8(1H)-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(((9aR)-2,2-dioxidohexahydropyrazino[2,1-c][1,4]thiazin-8(1H)-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-	815.1

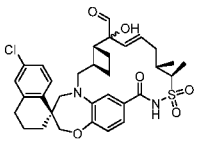
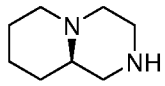
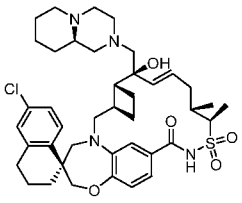
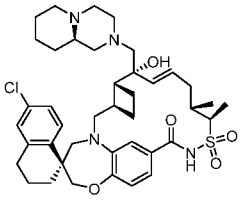
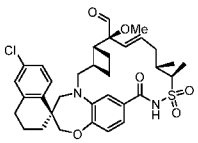
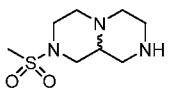
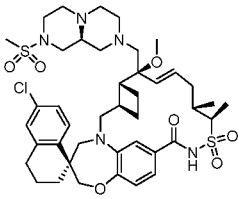
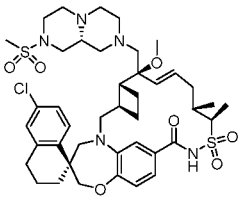
				dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
233		10	 AND	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aR)-8-(3-(phenylsulfonyl)propanoyl)octahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aS)-8-(3-(phenylsulfonyl)propanoyl)octahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	963.7
234	 AND	Example 276	 AND	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-7'-(((9aR)-8-acryloyloctahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-6-chloro-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,8'E,11'S,12'R)-7'-(((9aS)-8-acryloyloctahydro-2H-	820.3

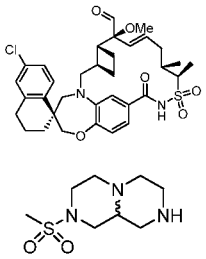
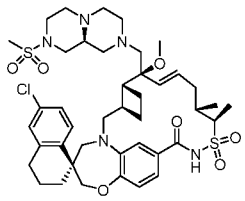
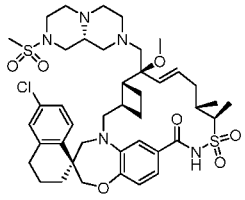
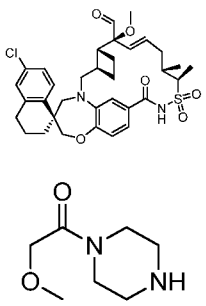
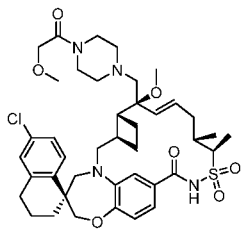
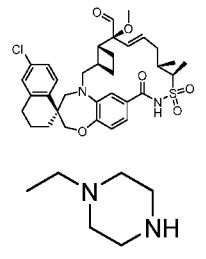
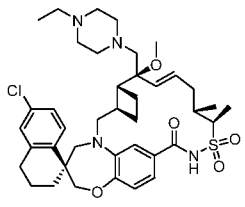
				pyrazino[1,2-a]pyrazin-2-yl)methyl)-6-chloro-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
235		10	 AND	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aR)-8-(1-methylethyl)octahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aS)-8-(1-methylethyl)octahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	828.0
236	 (J&W PharmLab)	10	 AND	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((9aR)-	751.4

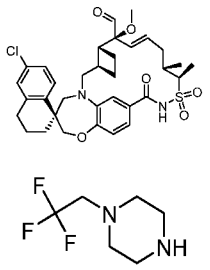
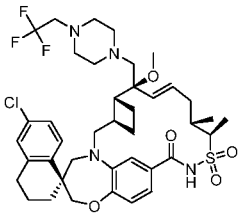
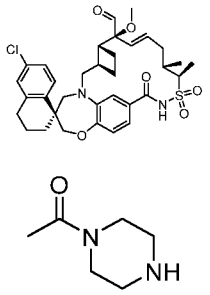
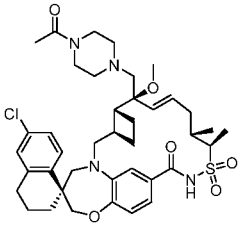
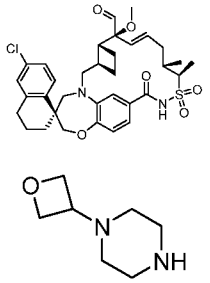
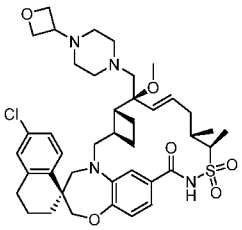
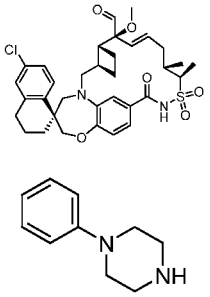
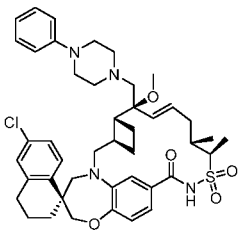
				octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
237		10	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aS)-8-(methylsulfonyl)octahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aR)-8-(methylsulfonyl)octahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	844.2
238		10	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aS)-8-(methylsulfonyl)octahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-	844.2

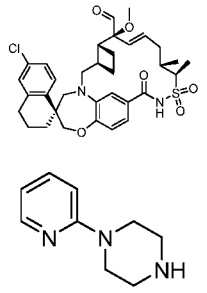
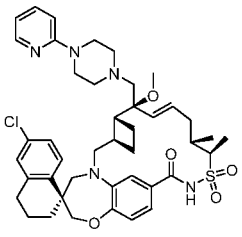
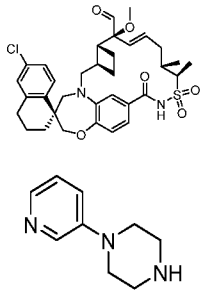
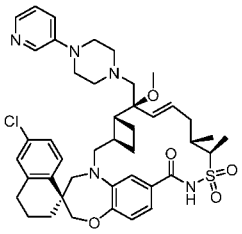
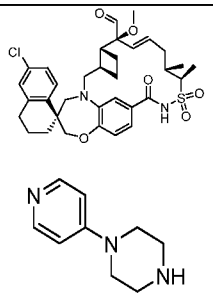
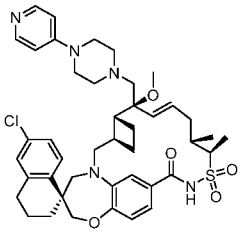
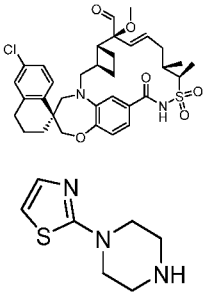
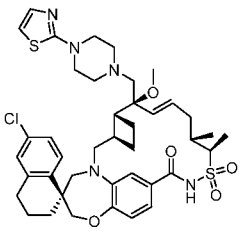
				methoxy-11',12'-dimethyl-7'-(((9aR)-8-(methylsulfonyl)octahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
239	  (Acros Organics)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-(1-methylethyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	753.7
240	 	10	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aS)-8-(1-methylethyl)octahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aR)-8-(1-methylethyl)octahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	809.0

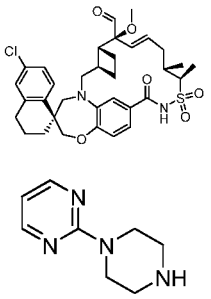
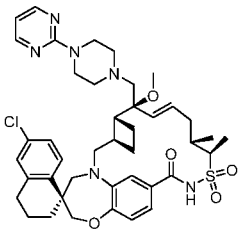
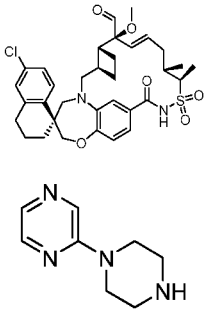
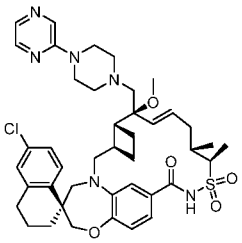
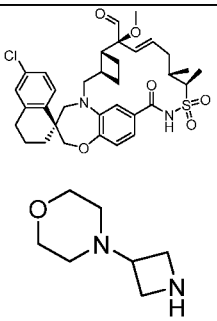
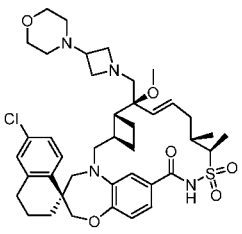
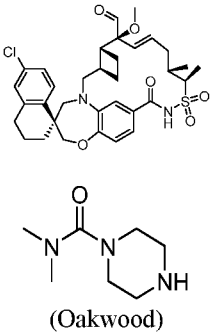
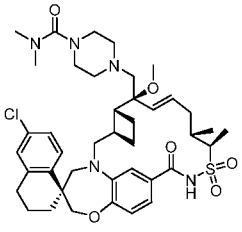
241		10	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aS)-8-(1-methylethyl)octahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aR)-8-(1-methylethyl)octahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	809.0
242	  (J&W PharmLab)	10	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,	751.4

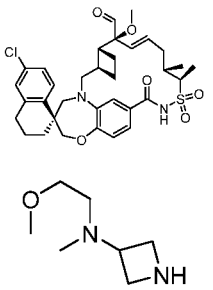
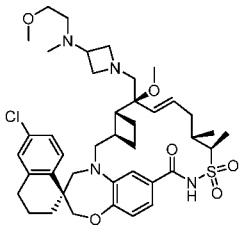
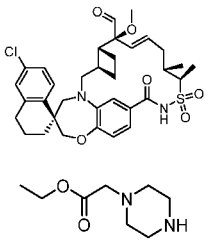
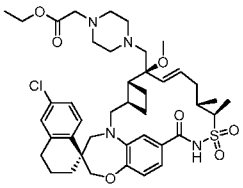
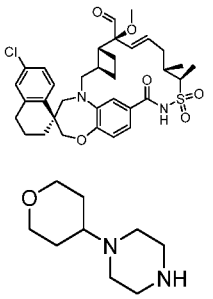
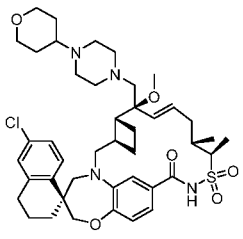
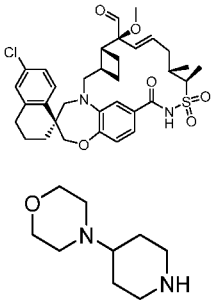
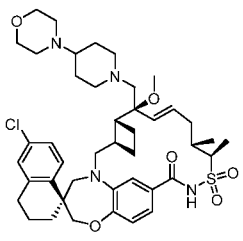
				24]tetraen]-15'-one 13',13'-dioxide	
243	  (J&W PharmLab)	10	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	751.4
244	 	10	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aS)-8-(methylsulfonyl)octahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aR)-8-(methylsulfonyl)octahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~	844.3

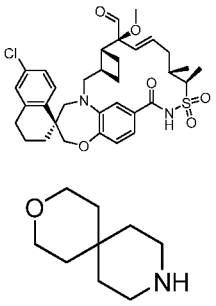
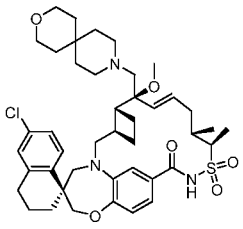
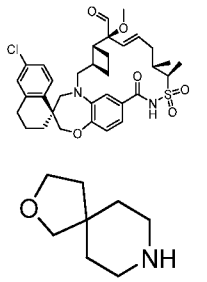
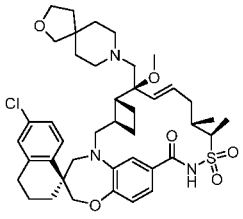
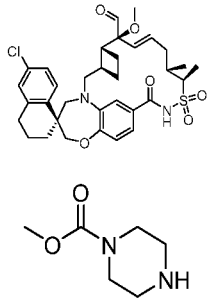
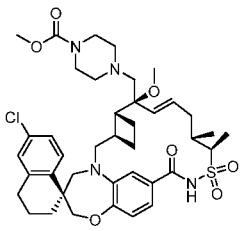
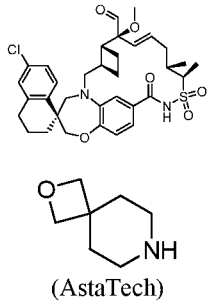
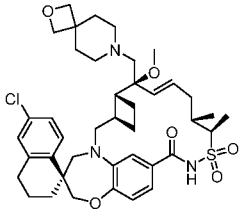
				19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
245		10	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aS)-8-(methylsulfonyl)octahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aR)-8-(methylsulfonyl)octahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	844.3
246	 (Enamine)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-7'-((4-(methoxyacetyl)-1-piperazinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	783.2
247		10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((4-ethyl-1-piperazinyl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	739.3

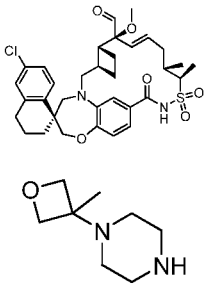
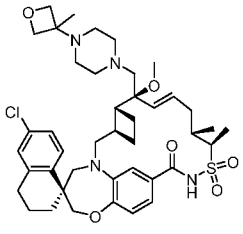
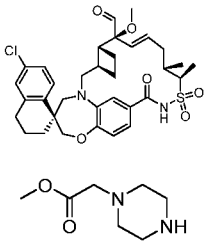
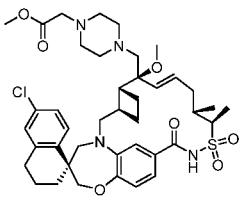
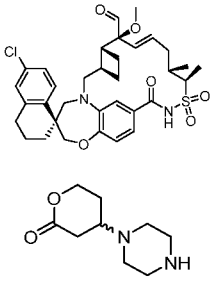
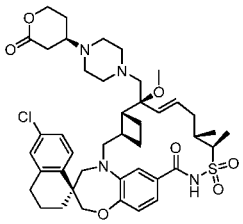
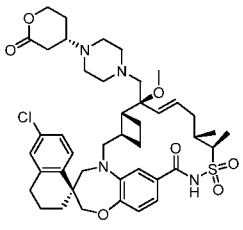
248	 (Enamine)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-(2,2,2-trifluoroethyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	793.2
249		10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-7'-((4-acetyl-1-piperazinyl)methyl)-6-chloro-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	753.3
250	 (Aurum)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-(3-oxetanyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	767.3
251	 (Alfa Aesar)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-phenyl-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	787.2

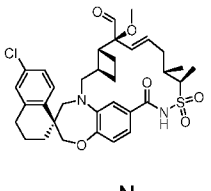
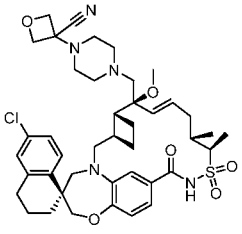
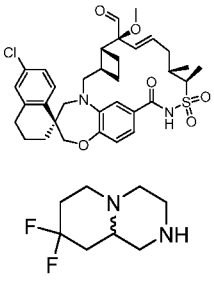
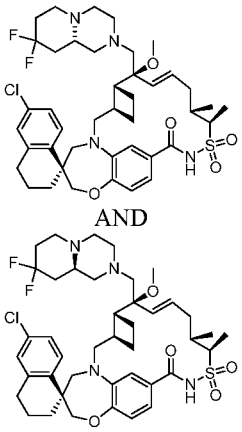
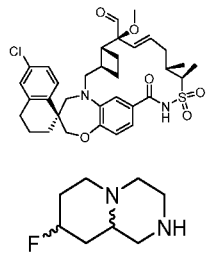
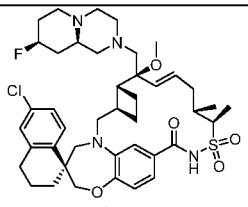
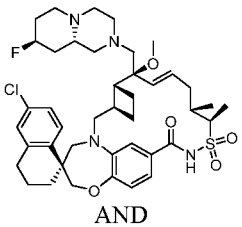
252		10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-(2-pyridinyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	788.8
253	 (Butt Park Ltd.)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-(3-pyridinyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	788.8
254	 (Lancaster Synthesis Ltd.)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-(4-pyridinyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	788.8
255	 (Enamine)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-(1,3-thiazol-2-yl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	794.8

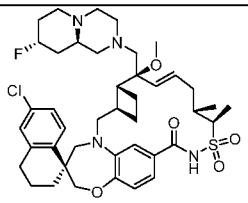
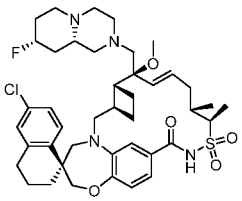
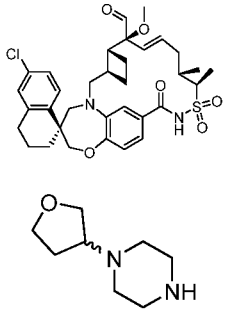
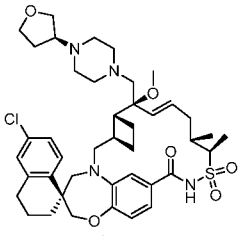
256		10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-(2-pyrimidinyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	789.9
257		10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-(2-pyrazinyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	789.0
258	 (ChemBridge Corporation)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((3-(4-morpholinyl)-1-azetidinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	767.8
259	 (Oakwood)	10		4-(((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)methyl)-N,N-dimethyl-1-piperazinecarboxamide	782.9

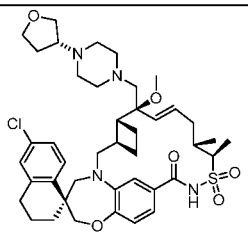
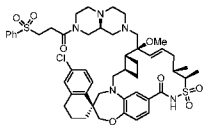
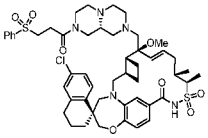
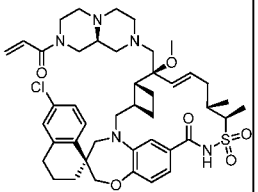
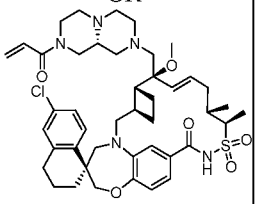
260	 (Ryan Scientific)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-7'-((3-((2-methoxyethyl)(methyl)amino)-1-azetidinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	769.8
261	 (Oakwood)	10		ethyl (4-(((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)methyl)-1-piperazinyl)acetate	797.0
262	 (AstaTech)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-(tetrahydro-2H-pyran-4-yl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	796.0
263	 (Oakwood)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-(4-morpholinyl)-1-piperidinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	796.0

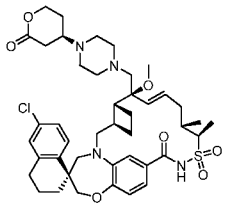
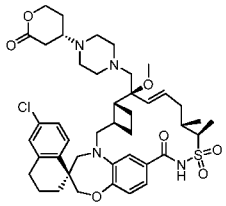
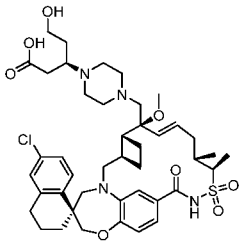
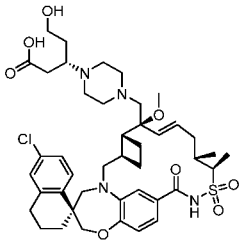
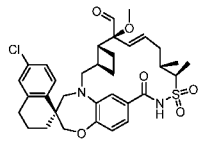
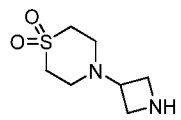
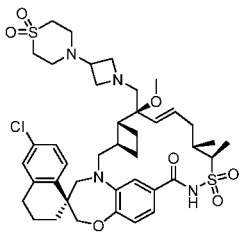
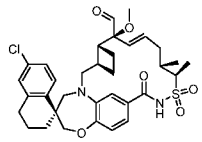
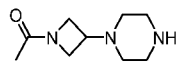
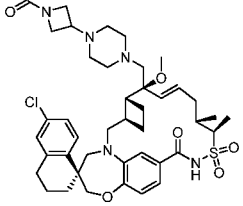
264	 (J&W PharmLab)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(3-oxa-9-azaspiro[5.5]undec-9-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	780.8
265	 (J&W PharmLab)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-oxa-8-azaspiro[4.5]dec-8-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	766.2
266		10		methyl 4-(((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)methyl)-1-piperazinecarboxylate	769.2
267	 (AstaTech)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-oxa-7-azaspiro[3.5]non-7-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	752.8

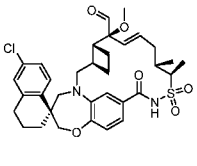
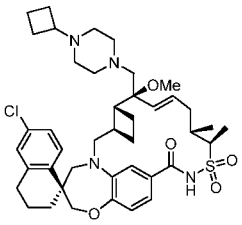
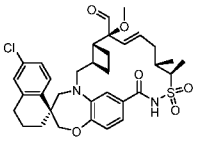
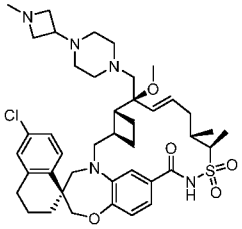
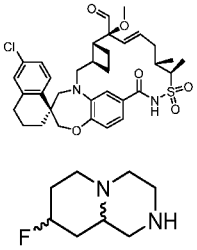
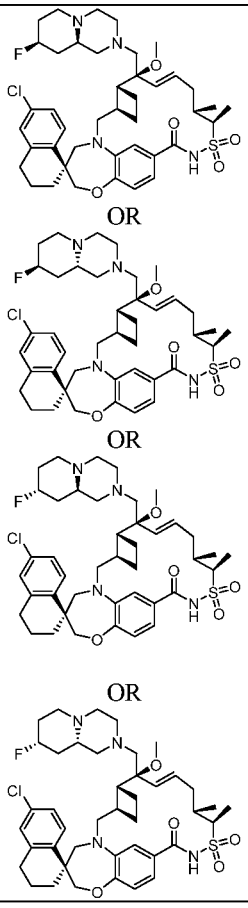
268	 (AstaTech)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-(3-methyl-3-oxetanyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	781.8
269		10		methyl (4-(((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)methyl)-1-piperazinyl)acetate	783.8
271		10	 AND 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-((4R)-2-oxotetrahydro-2H-pyran-4-yl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-((4S)-2-oxotetrahydro-2H-pyran-4-yl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	810.0

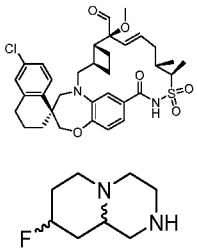
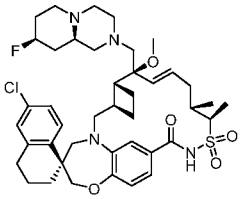
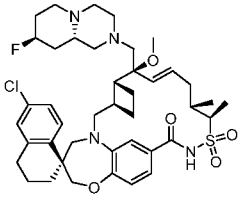
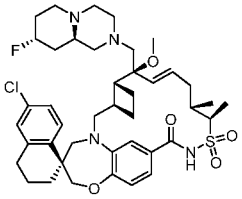
272	 (ChemShuttle)	10		3-(4-(((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)methyl)-1-piperazinyl)-3-oxetanecarbonitrile	792.8
273		10	 AND	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(((9aR)-8,8-difluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(((9aS)-8,8-difluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	801.9
274		10	 AND  AND	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(((8R,9aR)-8-fluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND	783.9

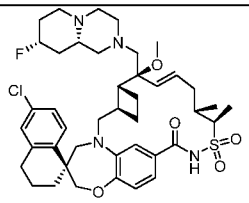
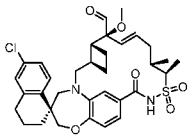
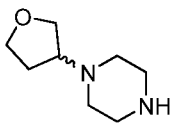
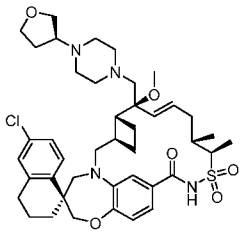
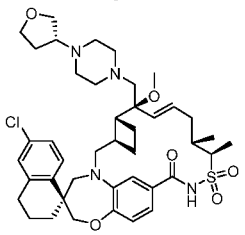
			 AND 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(((8R,9aS)-8-fluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(((8S,9aR)-8-fluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(((8S,9aS)-8-fluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
275		10	 AND	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-((3R)-tetrahydro-3-furanyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,	781.8

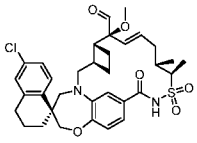
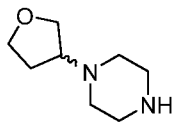
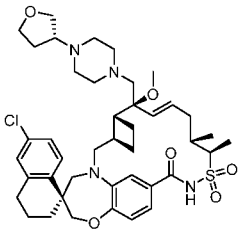
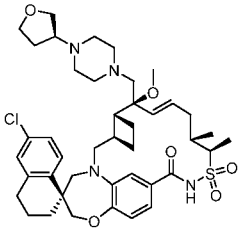
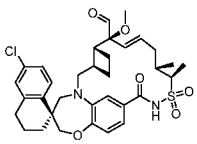
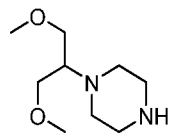
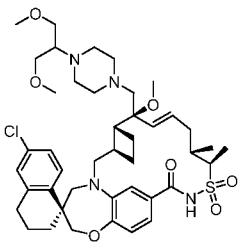
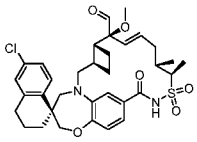
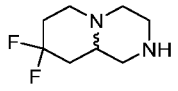
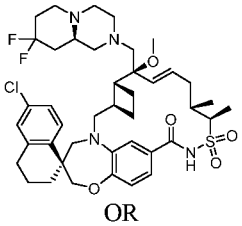
	(Manchester Organics Ltd.)			24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-((3S)-tetrahydro-3-furanyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
277	 OR 	See example 276	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-7'-(((9AR)-8-ACRYLOYLOCTAHYDRO-2H-PYRAZINO[1,2-A]PYRAZIN-2-YL)METHYL)-6-CHLORO-7'-METHOXY-11',12'-DIMETHYL-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[8,16,18,24]TETRAEN]-15'-ONE 13',13'-DIOXIDE OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-7'-(((9AS)-8-ACRYLOYLOCTAHYDRO-2H-PYRAZINO[1,2-A]PYRAZIN-2-YL)METHYL)-6-CHLORO-7'-METHOXY-11',12'-DIMETHYL-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[8,16,18,24]TETRAEN]-15'-ONE 13',13'-DIOXIDE	821.0

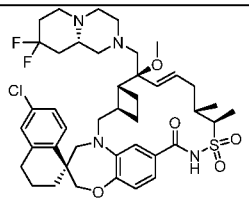
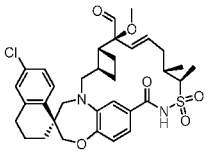
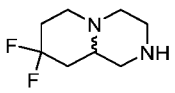
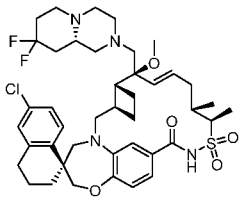
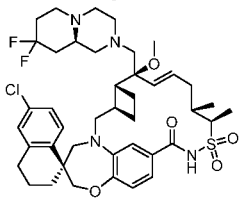
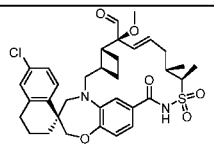
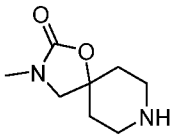
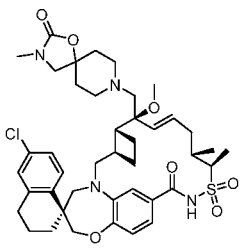
278	 AND 	Aqueous hydrolysis of lactone	 AND 	(3R)-3-(4-(((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)methyl)-1-piperazinyl)-5-hydroxypentanoic acid AND (3S)-3-(4-(((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)methyl)-1-piperazinyl)-5-hydroxypentanoic acid	828.0
279	  (Activate Scientific GmbH)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((3-(1,1-dioxido-4-thiomorpholinyl)-1-azetidinyl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	815.1
280	  (ChemShuttle)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-7'-((4-(1-acetyl-3-azetidinyl)-1-piperazinyl)methyl)-6-chloro-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	808.2

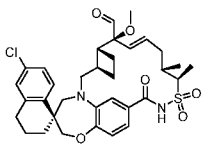
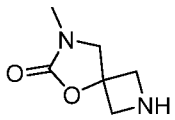
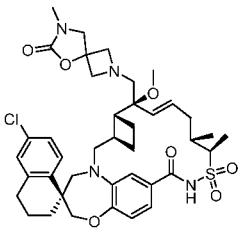
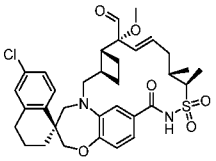
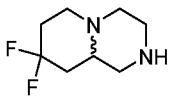
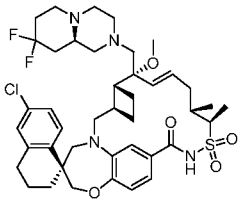
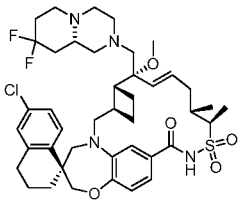
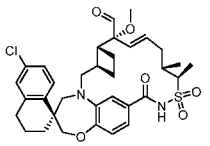
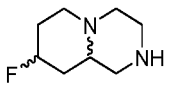
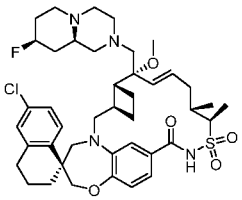
281	 (AstaTech)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((4-cyclobutyl-1-piperazinyl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	765.3
282	 (ChemShuttle)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-(1-methyl-3-azetidinyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	780.2
283		10	 OR OR OR	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(((8R,9aR)-8-fluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(((8R,9aS)-8-fluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR	783.9

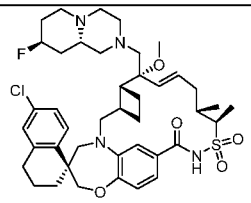
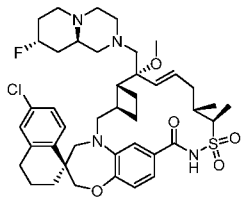
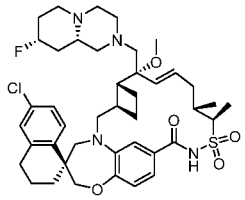
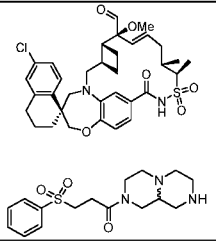
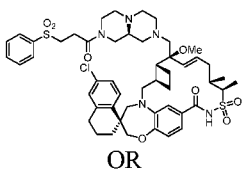
				(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(((8S,9aR)-8-fluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(((8S,9aS)-8-fluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
284		10	 OR  OR  OR	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(((8R,9aR)-8-fluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(((8R,9aS)-8-fluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~	783.9

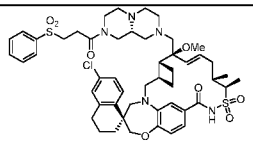
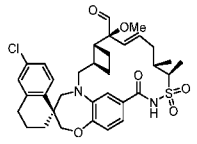
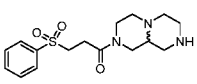
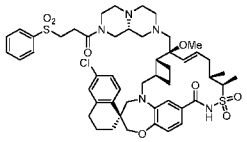
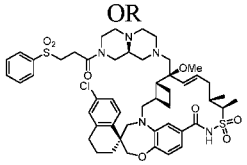
				19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(((8S,9aR)-8-fluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide Or (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(((8S,9aS)-8-fluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
285	  (Manchester Organics Ltd.)	10	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-((3S)-tetrahydro-3-furanyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-((3R)-tetrahydro-3-furanyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazat	781.3

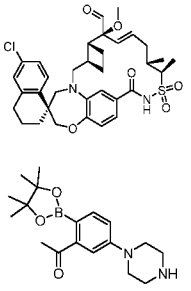
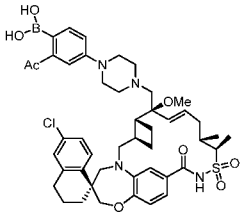
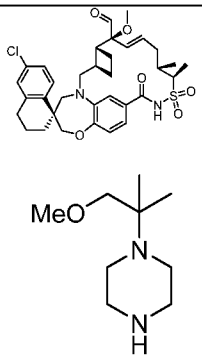
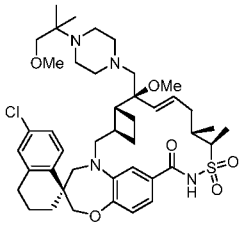
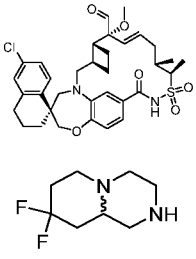
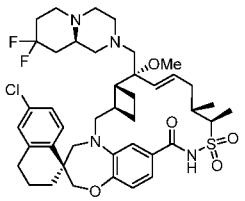
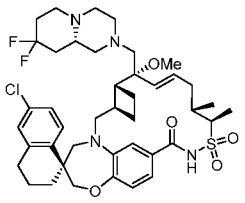
				etracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
286	  (Manchester Organics Ltd.)	10	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-((3S)-tetrahydro-3-furanyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-((3R)-tetrahydro-3-furanyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	781.3
287	  (FCH)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-7'-((4-(2-methoxy-1-(methoxymethyl)ethyl)-1-piperazinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	814.0
288	 	10	 OR	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(((9aR)-8,8-difluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,	801.9

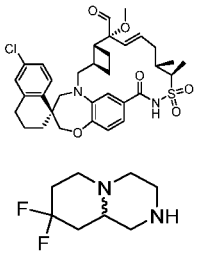
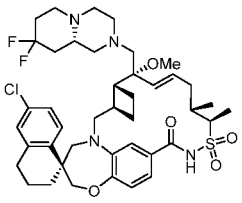
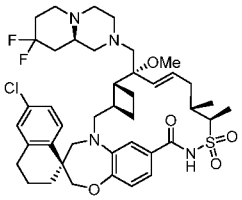
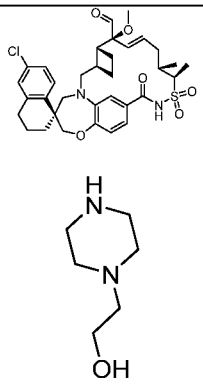
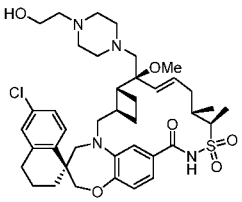
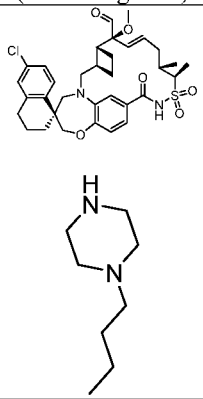
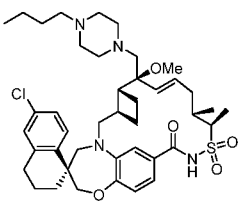
				24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(((9aS)-8,8-difluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
289	 	10	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(((9aR)-8,8-difluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(((9aS)-8,8-difluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	801.9
290	  (J&W PharmLab)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((3-methyl-2-oxo-1-oxa-3,8-diazaspiro[4.5]dec-8-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,	795.9

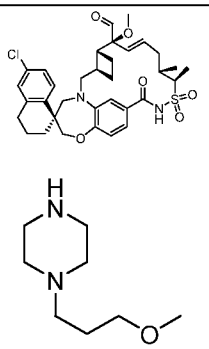
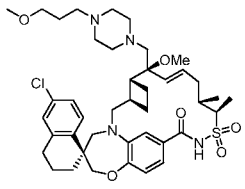
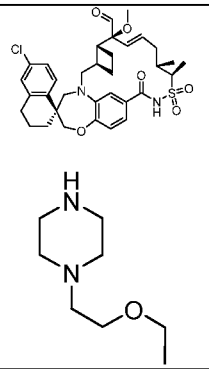
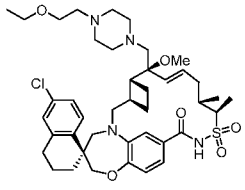
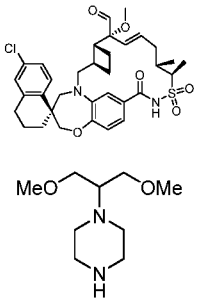
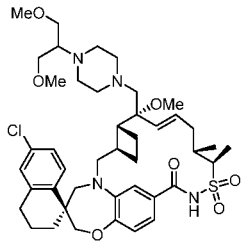
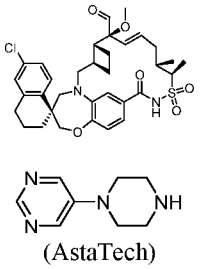
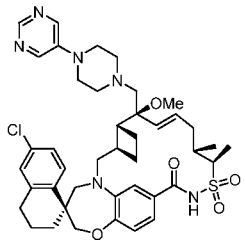
				24]tetraen]-15'-one 13',13'-dioxide	
291	  (FCH)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((7-methyl-6-oxo-5-oxa-2,7-diazaspiro[3.4]oct-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	767.8
292	 	10	 AND 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(((9aR)-8,8-difluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(((9aS)-8,8-difluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	801.9
293	 	10	 AND	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(((8R,9aR)-8-fluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,	783.9

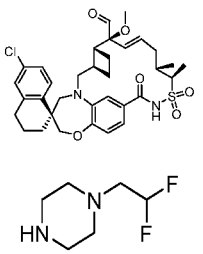
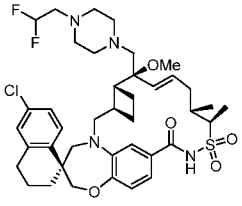
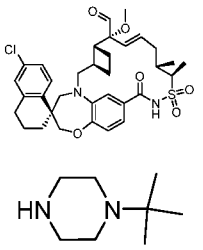
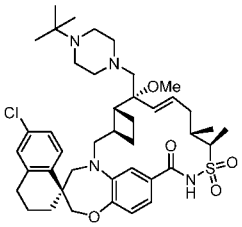
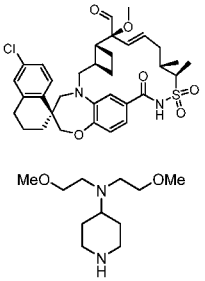
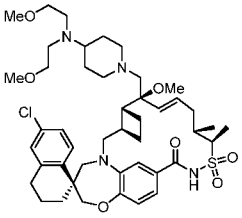
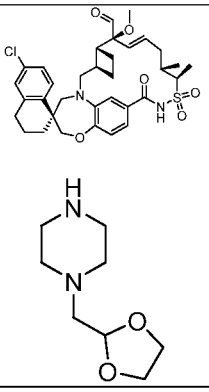
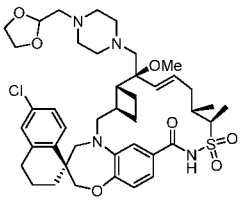
			 AND  AND 	24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(((8R,9aS)-8-fluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(((8S,9aR)-8-fluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(((8S,9aS)-8-fluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
294		10	 OR	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aS)-8-(3-(phenylsulfonyl)propanoyl)octahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-	962.2

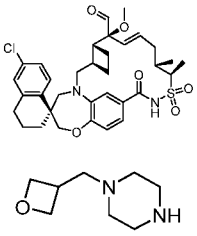
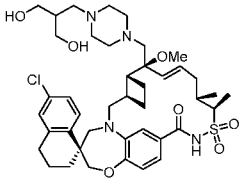
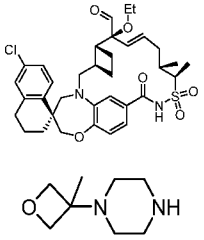
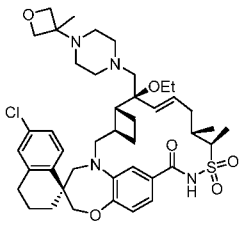
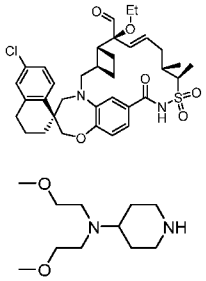
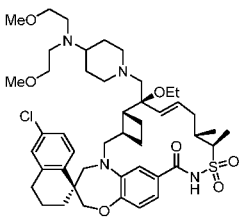
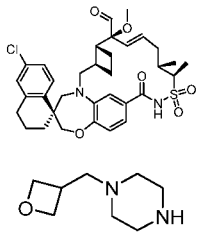
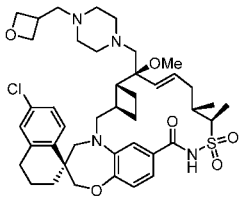
				2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aR)-8-(3-(phenylsulfonyl)propanoyl)octahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
295	 	10	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aS)-8-(3-(phenylsulfonyl)propanoyl)octahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((9aR)-8-(3-(phenylsulfonyl)propanoyl)octahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	962.2

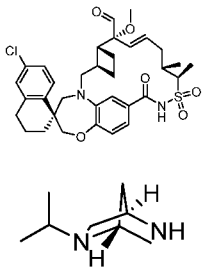
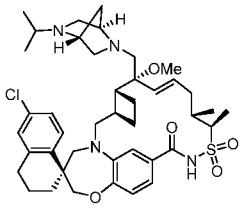
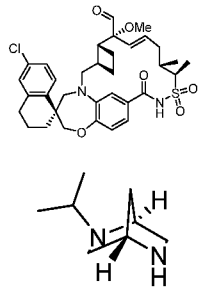
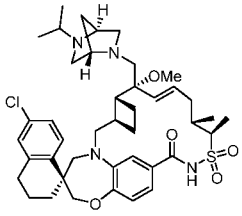
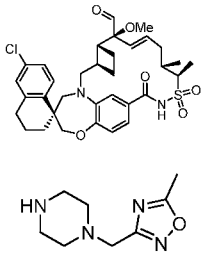
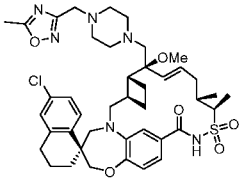
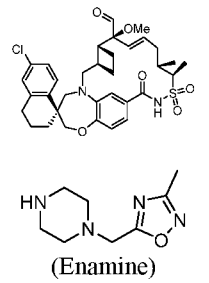
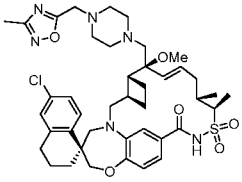
296		10 (in situ hydrolysis of boronate ester)		(2-acetyl-4-(4-(((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)methyl)-1-piperazinyl)phenyl)boronic acid	873.2
297	 (Enamine)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-7'-((4-(2-methoxy-1,1-dimethylethyl)-1-piperazinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	797.2
298		10	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(((9aR)-8,8-difluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(((9aS)-8,8-difluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	801.9

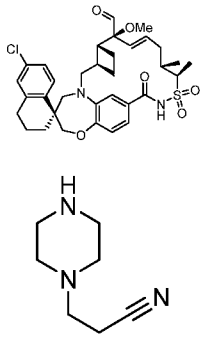
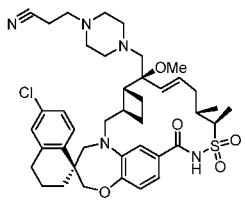
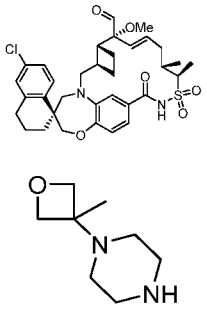
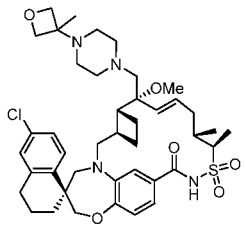
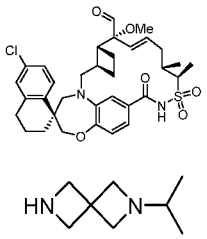
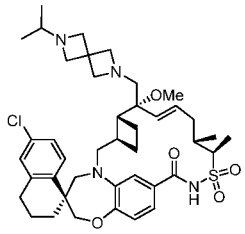
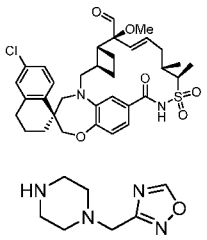
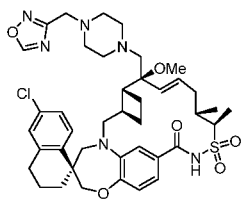
299		10	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(((9aS)-8,8-difluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(((9aR)-8,8-difluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	801.9
300	 (Acros Organics)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((4-(2-hydroxyethyl)-1-piperazinyl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	755.2
301		10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-7'-((4-butyl-1-piperazinyl)methyl)-6-chloro-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	767.3

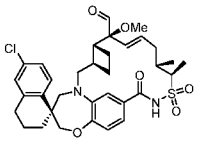
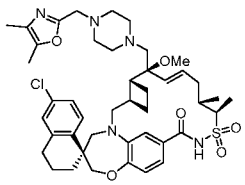
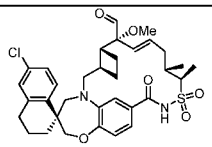
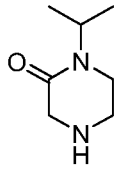
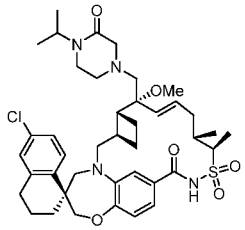
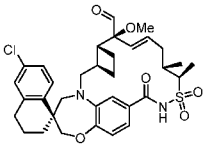
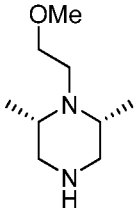
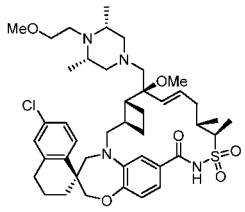
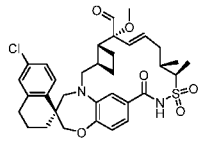
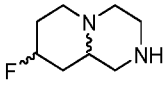
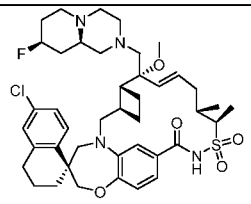
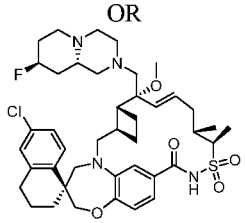
302		10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-7'-((4-(3-methoxypropyl)-1-piperazinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	783.2
303		10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((4-(2-ethoxyethyl)-1-piperazinyl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	783.3
304	 (FCH)	10		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-7'-((4-(2-methoxy-1-(methoxymethyl)ethyl)-1-piperazinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	813.2
305	 (AstaTech)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-(5-pyrimidinyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	789.9

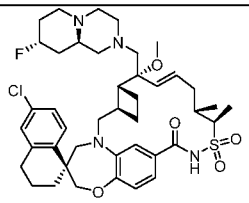
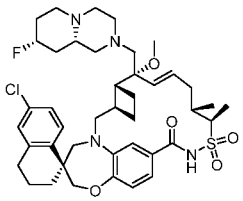
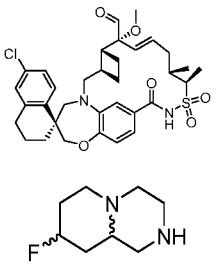
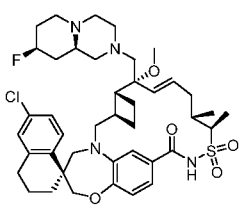
306	 (Enamine)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((4-(2,2-difluoroethyl)-1-piperazinyl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	775.8
307		10		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-7'-((4-tert-butyl-1-piperazinyl)methyl)-6-chloro-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	767.8
308	 (Enamine)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-7'-((4-(bis(2-methoxyethyl)amino)-1-piperidinyl)methyl)-6-chloro-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	842.1
309		10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((4-(1,3-dioxolan-2-ylmethyl)-1-piperazinyl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	797.9

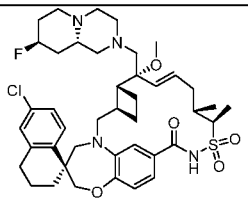
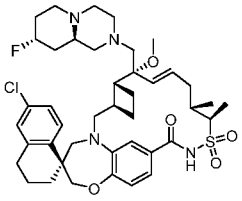
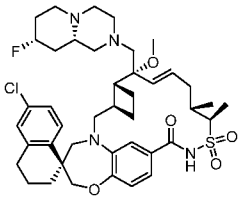
310		10 (with in situ oxetane hydrolysis)		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((4-(3-hydroxy-2-(hydroxymethyl)propyl)-1-piperazinyl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	800.0
311	 (AstaTech)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-ethoxy-11',12'-dimethyl-7'-((4-(3-methyl-3-oxetanyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	796.0
312	 (Enamine)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-7'-((4-(bis(2-methoxyethyl)amino)-1-piperidinyl)methyl)-6-chloro-7'-ethoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	856.2
313		10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-(3-oxetanylmethyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	781.8

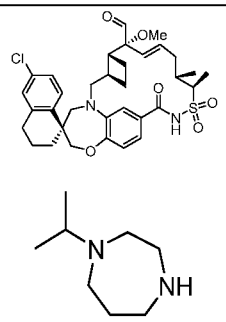
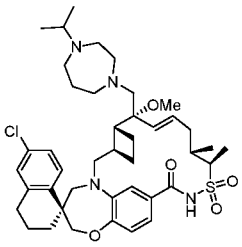
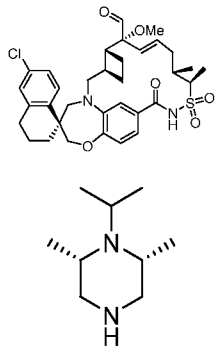
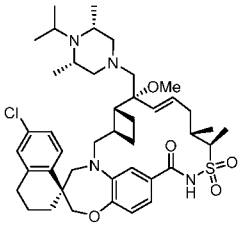
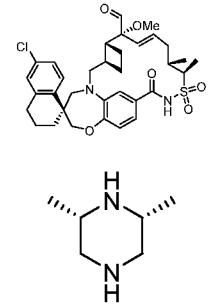
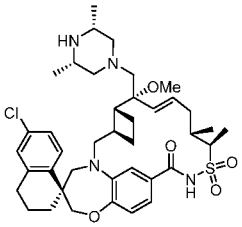
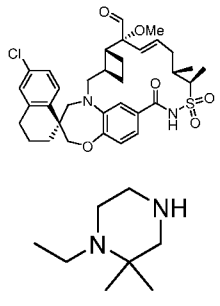
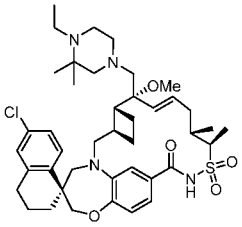
314		10		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((1R,4R)-5-(1-methylethyl)-2,5-diazabicyclo[2.2.1]hept-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	765.8
315		10		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((1S,4S)-5-(1-methylethyl)-2,5-diazabicyclo[2.2.1]hept-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	765.8
316	 (Enamine)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-((5-methyl-1,2,4-oxadiazol-3-yl)methyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	807.9
317	 (Enamine)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-((3-methyl-1,2,4-oxadiazol-5-yl)methyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	807.9

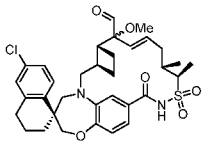
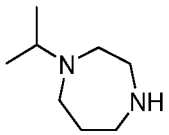
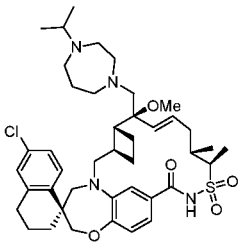
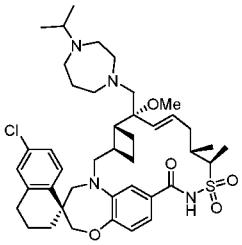
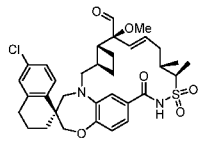
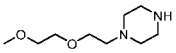
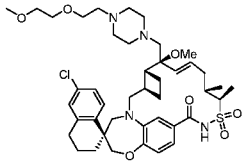
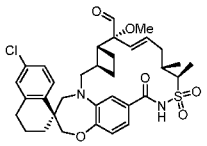
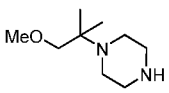
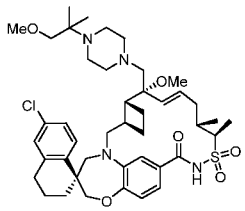
318		10		3-(4-(((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)methyl)-1-piperazinyl)propanenitrile	764.8
319	 (AstaTech)	10		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-(3-methyl-3-oxetanyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	782.0
320	 (ChemBridge)	10		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((6-(1-methylethyl)-2,6-diazaspiro[3.3]hept-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	765.9
321	 (Enamine)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-(1,2,4-oxadiazol-3-ylmethyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	793.2

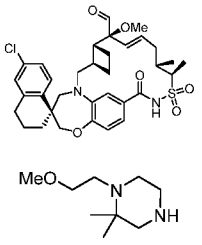
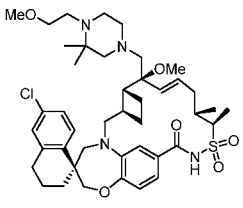
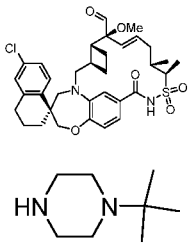
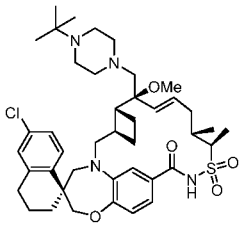
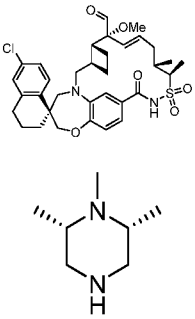
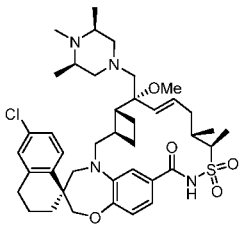
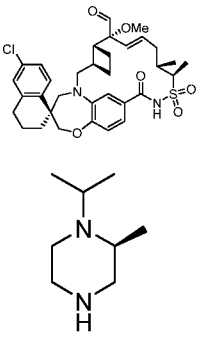
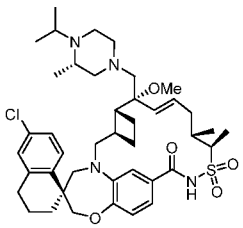
322	 (Enamine)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((4-((4,5-dimethyl-1,3-oxazol-2-yl)methyl)-1-piperazinyl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	820.3
323	  (Enamine)	10		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-(1-methylethyl)-3-oxo-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	767.3
324	 	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-7'-(((3R,5S)-4-(2-methoxyethyl)-3,5-dimethyl-1-piperazinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	797.3
325	 	10	 OR  OR	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(((8R,9aR)-8-fluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR	783.9

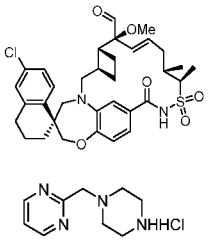
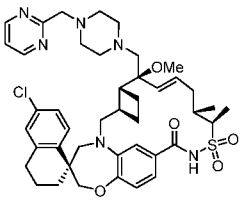
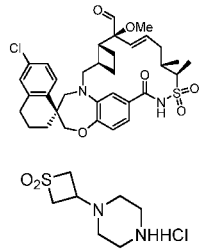
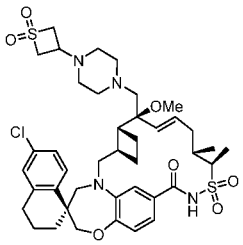
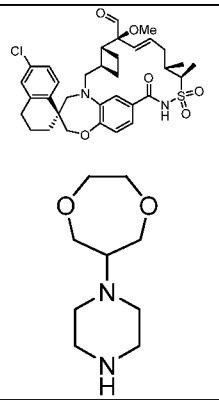
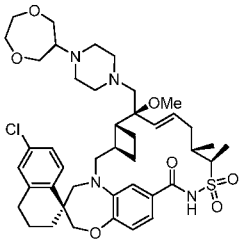
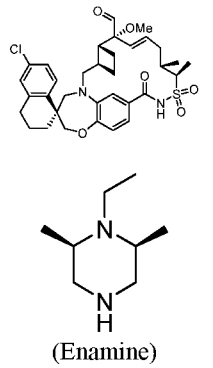
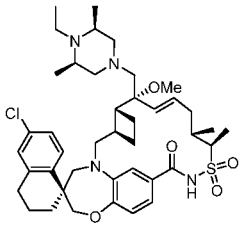
			 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(((8R,9aS)-8-fluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(((8S,9aR)-8-fluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(((8S,9aS)-8-fluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
326		10	 OR	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(((8R,9aR)-8-fluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~	783.9

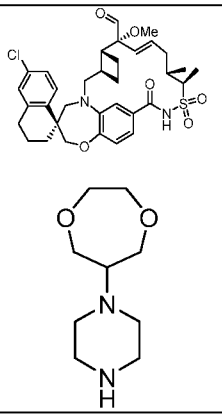
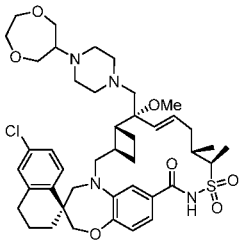
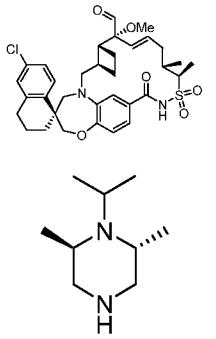
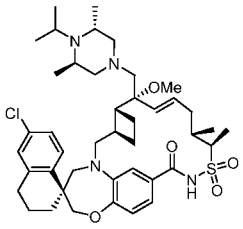
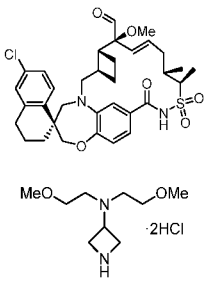
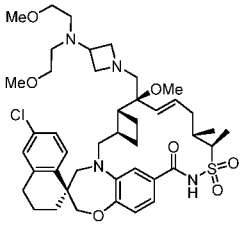
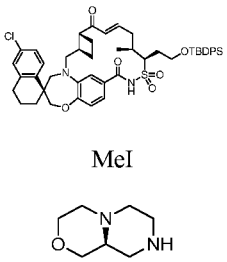
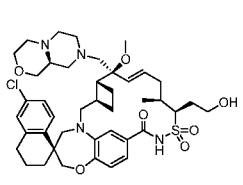
			 OR  OR 	19,24~]pentacosa[8,16,18, 24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S, 12'R)-6-chloro-7'-(((8R,9aS)-8-fluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18, 24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S, 12'R)-6-chloro-7'-(((8S,9aR)-8-fluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18, 24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S, 12'R)-6-chloro-7'-(((8S,9aS)-8-fluorooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18, 24]tetraen]-15'-one 13',13'-dioxide	

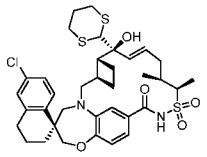
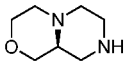
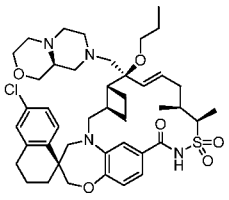
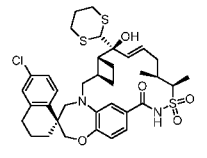
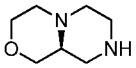
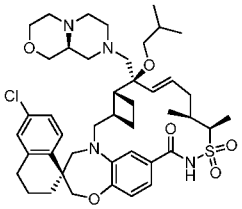
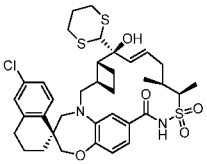
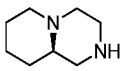
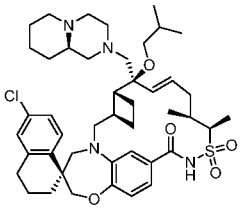
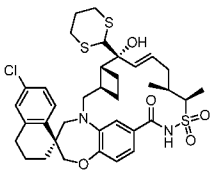
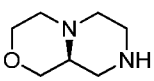
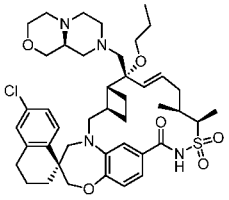
327	 (Enamine)	10		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-(1-methylethyl)-1,4-diazepan-1-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	767.3
328		10		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(((3R,5S)-3,5-dimethyl-4-(1-methylethyl)-1-piperazinyl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	781.3
329		10		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(((3R,5S)-3,5-dimethyl-1-piperazinyl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	739.2
330		10		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((4-ethyl-3,3-dimethyl-1-piperazinyl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	767.2

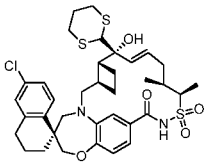
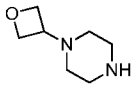
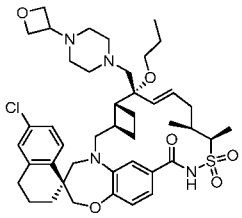
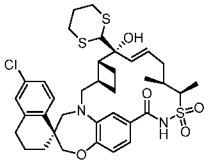
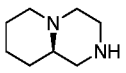
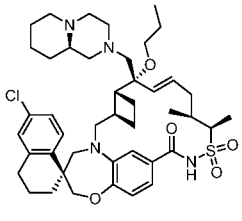
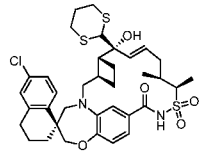
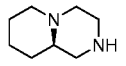
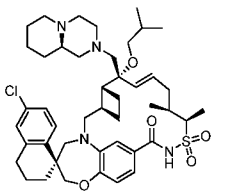
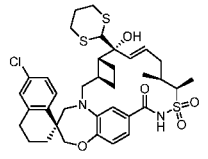
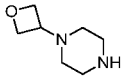
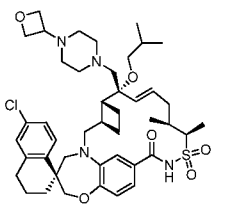
331	  (Enamine)	10	 AND 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-(1-methylethyl)-1,4-diazepan-1-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-(1-methylethyl)-1,4-diazepan-1-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	767.2
332	  (Enamine)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-7'-((4-(2-(2-methoxyethoxy)ethyl)-1-piperazinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	813.2
333	  (Enamine)	10		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-7'-((4-(2-methoxy-1,1-dimethylethyl)-1-piperazinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	797.2

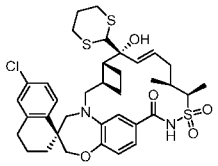
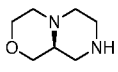
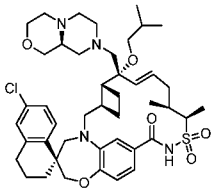
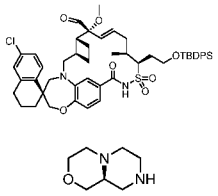
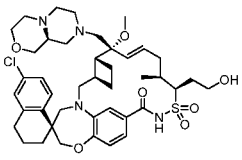
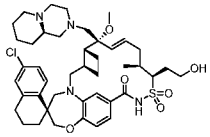
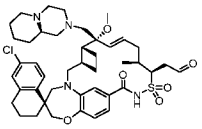
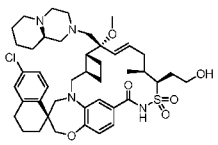
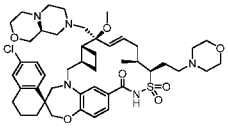
334	 (ChemShuttle)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-7'-((4-(2-methoxyethyl)-3,3-dimethyl-1-piperazinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	797.2
335	 (Oakwood)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-7'-((4-tert-butyl-1-piperazinyl)methyl)-6-chloro-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	767.2
336	 (Synthonix)	10		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((3R,5S)-3,4,5-trimethyl-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	753.2
337		10		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((3S)-3-methyl-4-(1-methylethyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	767.2

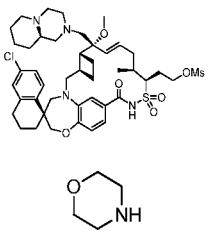
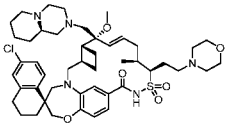
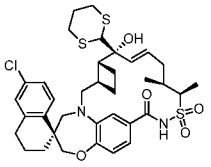
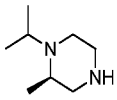
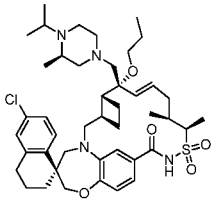
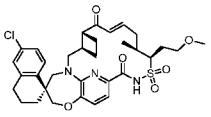
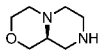
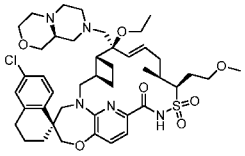
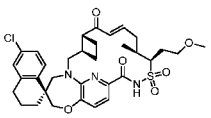
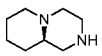
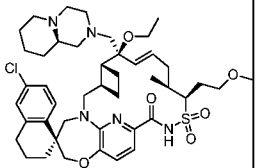
338	 (OxChem)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-(2-pyrimidinylmethyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	803.2
339	 (Ocatava)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((4-(1,1-dioxido-3-thietanyl)-1-piperazinyl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	815.2
340		10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((4-(1,4-dioxepan-6-yl)-1-piperazinyl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	811.2
341	 (Enamine)	10		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(((3R,5S)-4-ethyl-3,5-dimethyl-1-piperazinyl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	767.2

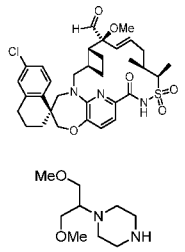
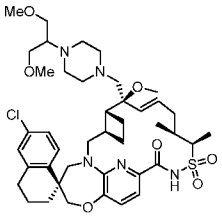
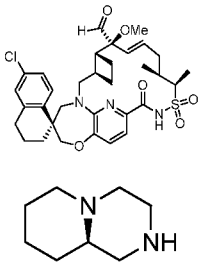
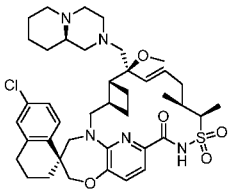
342		10		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((4-(1,4-dioxepan-6-yl)-1-piperazinyl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	811.2
343		10		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(((3R,5R)-3,5-dimethyl-4-(1-methylethyl)-1-piperazinyl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	781.2
344	 (FCH)	10		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-7'-((3-(bis(2-methoxyethyl)amino)-1-azetidinyl)methyl)-6-chloro-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	813.2
346	 MeI	5, 9 Example 367, (Step 11)		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-12'-(2-hydroxyethyl)-7'-methoxy-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	797.2

347	 n-Propyl Iodide 	5, 9		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-11',12'-dimethyl-7'-propoxy-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	795.3
349	 3-bromo-2-methylprop-1-ene 	5, Example 348 (Step 2), 9		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-11',12'-dimethyl-7'-(2-methylpropoxy)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	809.2
350	 3-bromo-2-methylprop-1-ene 	5, Example 348 (Step 2), 8		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-7'-(2-methylpropoxy)-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	807.4
351	 allyl bromide 	5, Example 348 (Step 2), 9		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-11',12'-dimethyl-7'-propoxy-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	795.3

352	 allyl bromide 	5, Example 348 (Step 2), 8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-7'-((4-(3-oxetanyl)-1-piperazinyl)methyl)-7'-propoxy-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	795.3
353	 allyl bromide 	5, Example 348 (Step 2), 8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-7'-propoxy-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	793.4
354	 3-bromo-2-methylprop-1-ene 	5, Example 348 (Step 2), 8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-7'-(2-methylpropoxy)-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	807.3
355	 3-bromo-2-methylprop-1-ene 	5, Example 348 (Step 2), 8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-7'-(2-methylpropoxy)-7'-((4-(3-oxetanyl)-1-piperazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	809.3

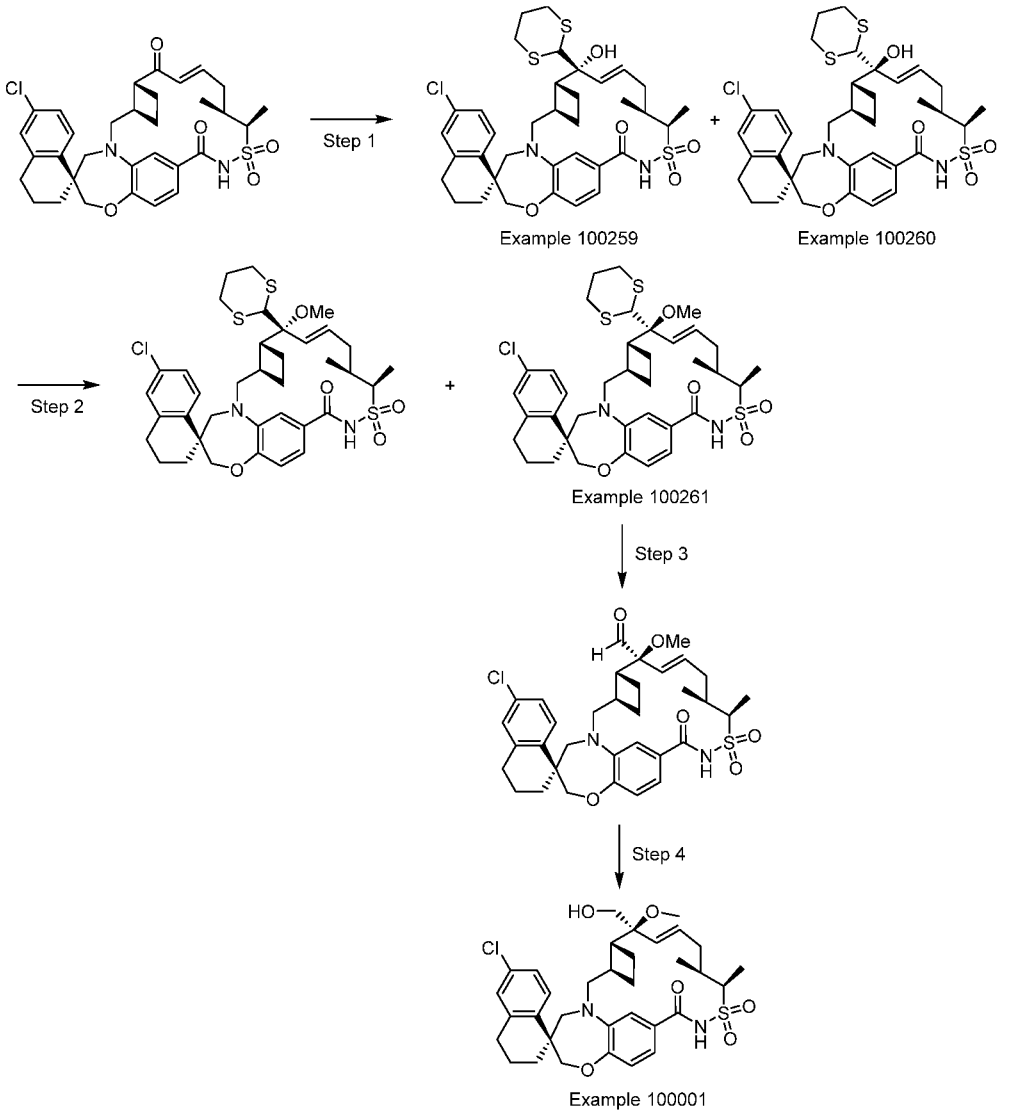
356	 3-bromo-2-methylprop-1-ene 	5, Example 348 (Step 2), 9		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-11',12'-dimethyl-7'-(2-methylpropoxy)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	809.4
357		9, Example 367 (Step 11)		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-12'-(2-hydroxyethyl)-7'-methoxy-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	797.4
360	 (Example 358)	See example 18 (Step 14)		((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11'-methyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-12'-yl)acetaldehyde	793.3
361	 (Example 346)	See example 367 (Steps 12, 13)		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7'-methoxy-11'-methyl-12'-(2-(4-morpholinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	866.4

365		See example 367 (Step 13)		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11'-methyl-12'-(2-(4-morpholinyl)ethyl)-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	864.3
368	 allyl bromide 	5, Example 348 (Step 2), 8		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-7'-(((3R)-3-methyl-4-(2-propanyl)-1-piperazinyl)methyl)-7'-propoxy-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	795.3
369	 EtI  (Pharmablock)	4, 8		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-ethoxy-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	826.2
370	 EtI 	4, 8		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-ethoxy-12'-(2-methoxyethyl)-11'-methyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	824.3

371	 (FCH Group)	8		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-7'-((4-(2-methoxy-1-(methoxymethyl)ethyl)-1-piperazinyl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	814.2
372	 (Aurum)	8		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	766.3

Example 100001

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(hydroxymethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide



Step 1: (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide and (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

To a 250 mL round-bottomed flask was added 1,3-dithiane (4.79 g, 39.8 mmol) and THF (100 mL). The mixture was cooled to -78 °C and n-butyllithium (1.6 M solution in hexane, 22.5 mL, 36.1 mmol) was added over 8 min. The solution was stirred in the -78 °C bath for 30 min. In a separate 100 mL flask was added (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,7'H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7',15'-dione 13',13'-dioxide and THF (5 mL). To this was added lanthanum(III) chloride bis lithium chloride complex solution (0.6 M in THF, 60.1 mL, 36.1 mmol) and this was stirred for 5 min at room temperature. The solution was then cooled to -78 °C and added via cannula to the dithiane solution. After 2.5 h at -78 °C, the solution was treated with sat NH_4Cl and water. The pH of the solution was adjusted to pH = 4 with aqueous 10% citric acid and aqueous $NaHCO_3$. The solution was extracted with EtOAc and the combined extracts were filtered through Celite. The extracts were washed with water and brine and then dried (Na_2SO_4) and concentrated to afford a mixture of (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide and (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide as a brown oil which was carried on directly to the next step. MS (ESI, +ve ion) *m/z* 717.5 $(M+H)^+$.

Step 2: (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide and (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-

spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

To a resealable vial was added the mixture of (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide and (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (6.81 g, 9.49 mmol) and THF (100 mL). The mixture was cooled to 0 °C and potassium bis(trimethylsilyl)amide (1 M in THF, 38.0 mL, 38.0 mmol) was added over 10 min. The solution was stirred at 0 °C for 5 min and then iodomethane (2.36 mL, 38.0 mmol) was added over 3 min. After 2.5 h at 0 °C, the solution was poured into saturated NH_4Cl and the pH was adjusted to 4 with 1 M citric acid. The solution was extracted with EtOAc and the combined extracts were washed with brine, dried (Na_2SO_4) and concentrated onto silica. Purification by silica gel chromatography (0% to 35% EtOAc/heptane, with 0.3% AcOH, 330 g Redi-Sep Gold column) afforded (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (1.66 g, 2.27 mmol, 24% yield). MS (ESI, +ve ion) *m/z* 731.5 $(M+H)^+$ and (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (4.69 g, 6.41 mmol, 68% yield). MS (ESI, +ve ion) *m/z* 731.5 $(M+H)^+$.

Step 3: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide

To a 250 mL round-bottomed flask equipped with a reflux condenser was added (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (1.63 g, 2.23 mmol), acetonitrile (40 mL) and water (10 mL). The mixture was heated to 50 °C and calcium carbonate (1.12 g, 11.1 mmol) and iodomethane (1.38 mL, 22.3 mmol) were added. After 23 h at 50 °C, the solution was poured into saturated NH_4Cl and water and then extracted with EtOAc. The combined extracts were washed with brine and then dried (Na_2SO_4) and concentrated onto silica. Purification by silica gel chromatography (0 to 40% EtOAc/heptane (both with 0.3% AcOH), Silicycle HP 120 g column) afforded (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide (1.34 g, 2.09 mmol, 94% yield) as a white solid. MS (ESI, +ve ion) *m/z* 641.3 $(M+H)^+$.

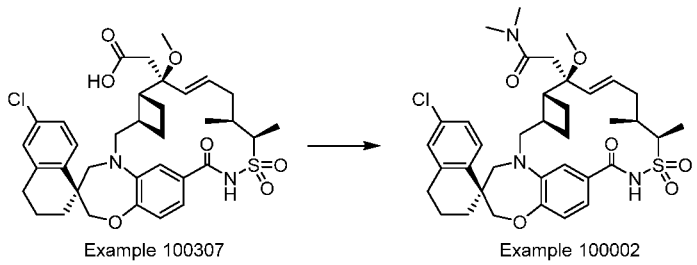
Step 4: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(hydroxymethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

To a room temperature solution of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide (30 mg, 0.047 mmol) in MeOH (2

mL) and THF (0.5 mL), was added sodium borohydride (17 mg, 0.47 mmol). After 5 min at rt the solution was poured into saturated NaCl and then extracted with EtOAc. The combined extracts were dried (Na_2SO_4) and concentrated. Purification by silica gel chromatography (0% to 60% EtOAc (0.3% AcOH) in heptane (4 g column)) afforded (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(hydroxymethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (10 mg, 0.016 mmol, 50% yield) as a white solid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.95-8.01 (m, 1H), 7.68 (d, *J*=8.61 Hz, 1H), 7.16-7.20 (m, 1H), 7.10 (dd, *J*=1.86, 13.99 Hz, 2H), 6.85-6.95 (m, 2H), 5.71-5.80 (m, 1H), 5.67 (d, *J*=0.98 Hz, 1H), 4.29-4.41 (m, 1H), 4.07 (d, *J*=4.89 Hz, 3H), 3.87-3.97 (m, 2H), 3.72 (br d, *J*=14.48 Hz, 1H), 3.26 (d, *J*=14.28 Hz, 1H), 3.10 (s, 3H), 2.96-3.04 (m, 1H), 2.72-2.80 (m, 2H), 2.56-2.65 (m, 1H), 2.44 (s, 1H), 1.75-2.28 (m, 9H), 1.55-1.71 (m, 1H), 1.50 (d, *J*=7.04 Hz, 3H), 1.50-1.41 (m, 1H), 1.06 (d, *J*=6.85 Hz, 3H). One exchangeable proton was not observed. MS (ESI, +ve ion) *m/z* 643.2 $(M+H)^+$.

Example 100002

2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-dimethylacetamide



Example 100307 Example 100002

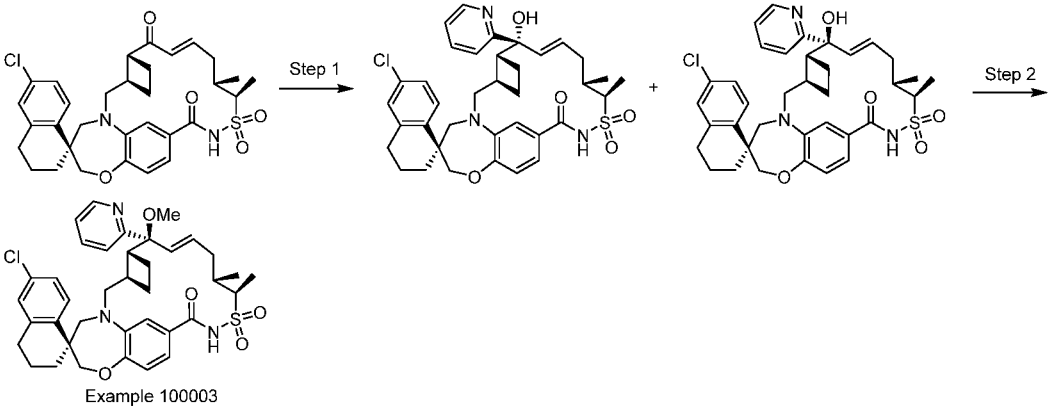
((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-

[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetic acid (60 mg, 0.089 mmol) was taken up in THF (1.8 mL) and lithium hydroxide (2.0 M in water, 0.18 mL, 0.36 mmol) was added. The mixture was stirred at room temperature for 10 min before being concentrated in vacuo to provide the lithium carboxylate of the starting material as an off-white solid that was used in the amide coupling. HATU (51.0 mg, 0.134 mmol) and dimethylamine (2.0 M in THF, 0.134 mL, 0.268 mmol) were added to a stirred suspension of the lithium carboxylate previously prepared in *N*,*N*-dimethylformamide (1.8 mL). The reaction mixture was stirred at room temperature for 10 minutes. The reaction mixture was diluted with water and EtOAc and transferred to a separatory funnel. 1.0 M HCl was added and the phases were mixed. The organic layer was separated and washed sequentially with 1.0 M LiCl and brine then dried over magnesium sulfate and concentrated under reduced pressure. Purification via silica gel flash chromatography using a gradient of 50% to 100% EtOAc + 0.3% AcOH in heptane afforded 2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-dimethylacetamide (38 mg, 0.054 mmol, 61% yield) as a white solid. ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.71 (d, *J*=8.48 Hz, 1 H) 7.17 (dd, *J*=8.77, 2.19 Hz, 1 H) 7.07 - 7.11 (m, 1 H) 7.01 - 7.04 (m, 1 H) 6.95 - 7.00 (m, 1 H) 6.88 - 6.93 (m, 1 H) 5.71 - 5.92 (m, 2 H) 4.00 - 4.11 (m, 3 H) 3.84 (br d, *J*=15.20 Hz, 1 H) 3.70 (br d, *J*=14.03 Hz, 1 H) 3.30 (d, *J*=14.32 Hz, 1 H) 3.17 (s, 3 H) 3.08 - 3.15 (m, 2 H) 3.06 (s, 3 H) 3.01 (s, 1 H) 2.94 (s, 3 H) 2.65 - 2.87 (m, 3 H) 2.39 - 2.65 (m, 3 H) 2.02 - 2.21 (m, 4 H) 1.51 - 1.97 (m, 11 H) 1.30 - 1.47 (m, 5 H) 1.05 (d, *J*=6.14 Hz, 3 H). MS (ESI, +ve) *m/z* 666.2 $[M - OMe]^+$.

Example 100003

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'

[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide



Example 100003

Step 1: (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

A solution of 2-bromopyridine (105 μL, 1.1 mmol) in THF (4 mL) was cooled to - 78 °C under nitrogen atmosphere. A solution of n-butyllithium in hexanes (2.5 M, 422 μL, 1.1 mmol) was added dropwise and the reaction mixture was stirred for 30 min. A solution of (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,7'H,15'H-spiro[naphthalene-1,22'[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7',15'-dione 13',13'-dioxide (300 mg, 0.5 mmol) in THF (1 mL) was added dropwise and the reaction mixture was allowed to warn to room temperature overnight. An aqueous saturated solution of NH_4Cl was added and the reaction mixture was extracted with EtOAc. The organic phase was separated, washed with brine and concentrated under reduced pressure. The yellow solid was

purified by column chromatography on silica gel, eluting with a gradient of 0 to 35% EtOAc (containing 0.3% HOAc)/hexane to obtain a mixture of (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide as a light-yellow solid (129 mg). The mixture was used in the next step without additional purification. MS (ESI, +ve ion) *m/z* 676.0 $(M+H)^+$.

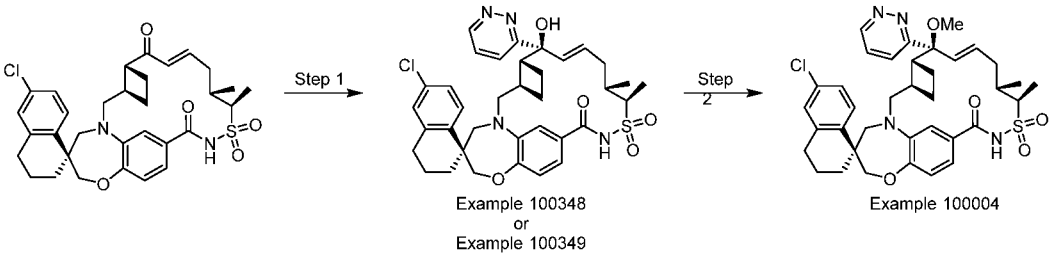
Step 2 : (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

The mixture of (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (129 mg, 0.19 mmol) was dissolved in THF (5 mL) and the solution was cooled with a water bath. Sodium hydride (60% dispersion in mineral oil, 201 mg, 5 mmol) was added in one portion. After 15 min, iodomethane (624 μL, 10 mmol) was added. An additional portion of each NaH and MeI were added after 2 h. An aqueous saturated solution of NH_4Cl was added and the reaction mixture was extracted with EtOAc The solvent was removed under reduced pressure. The concentrate was purified by preparative

reversed-phase preparative HPLC using a Phenomenex Gemini column, 10 μm, C18, 110 Å, 100 x 50 mm, 0.1% TFA in CH_3CN/H_2O, gradient 10% to 100% over 20 min to afford 21 mg of [(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide, the second eluting peak, as a white solid. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.15 (m, 3 H) 1.24 - 1.34 (m, 2 H) 1.48 (m, 3 H) 1.61 - 1.80 (m, 2 H) 1.83 - 1.93 (m, 2 H) 1.95 - 2.07 (m, 3 H) 2.19 - 2.32 (m, 3 H) 2.62 - 2.82 (m, 5 H) 3.06 (s, 3 H) 3.11 - 3.21 (m, 2 H) 3.70 (m, 1 H) 3.96 - 4.01 (m, 1 H) 4.04 - 4.09 (m, 1 H) 4.17 (m, 1 H) 5.86 - 6.02 (m, 2 H) 6.92 - 6.97 (m, 1 H) 6.99 - 7.03 (m, 1 H) 7.09 (d, *J*=8.02 Hz, 2 H) 7.18 (dd, *J*=8.41, 1.96 Hz, 1 H) 7.65 - 7.71 (m, 2 H) 8.34 - 8.40 (m, 2 H) 9.02 (d, *J*=5.09 Hz, 1 H). MS (ESI, +ve ion) *m/z* 690.0 $(M+H)^+$.

Example 100004

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(3-pyridazinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide



Step 1: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(3-pyridazinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

To a solution of 2,2,6,6-tetramethylpiperidine (1.06 mL, 6.3 mmol) in THF (28 mL) that was cooled to 0 °C was added a solution of n-butyllithium (2.5 M in THF, 2.4 mL, 6.0 mmol) under nitrogen atmosphere. The reaction was stirred at 0 °C for 25 minutes then cooled to -78 °C. A solution of pyridazine (110 μL, 1.5 mmol) in THF (5 mL) was added dropwise, followed by a solution of (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,7'H,15'H-spiro[naphthalene-1,22'[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7',15'-dione 13',13'-dioxide (300 mg, 0.502 mmol) in THF (3 mL). The reaction mixture was allowed to stir at -78 °C for 2 h and quenched by the addition of aqueous saturated ammonium chloride solution. The reaction mixture was extracted with EtOAc. The organic phase was separated, washed with brine and concentrated under reduced pressure to give the crude material. The crude material was purified by silica gel flash chromatography using a gradient of 50% to 100% EtOAc + 0.3% AcOH in heptane to provide 106 mg of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(3-pyridazinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide, the second eluting peak. MS (ESI, +ve ion) *m/z* 677.0 $(M+H)^+$.

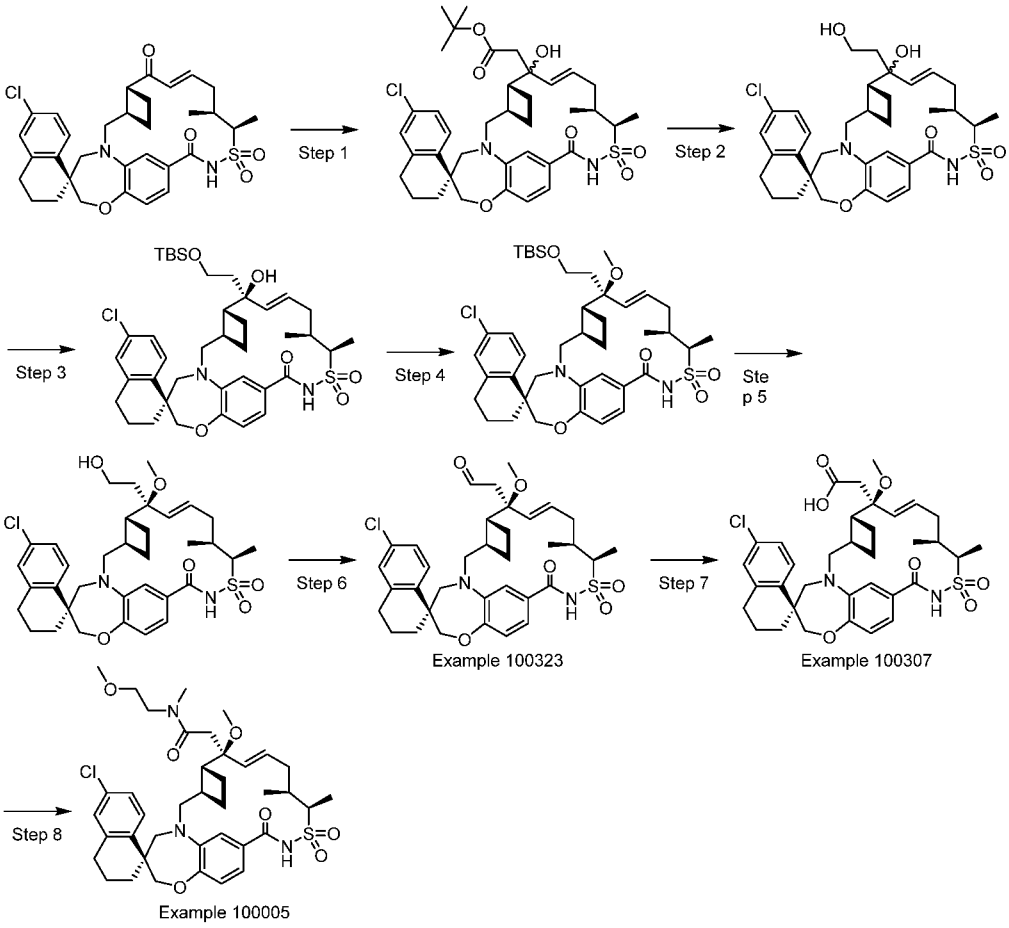
Step 2: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(3-pyridazinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

Sodium hydride (60% dispersion in mineral oil, 81 mg, 2.0 mmol) was added in one portion to a solution of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(3-pyridazinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (137 mg, 0.2 mmol) in tetrahydrofuran (6.7

mL). After 5 min, iodomethane (251 µL, 4.1 mmol) was added and the reaction was stirred for 2 hours. MeOH (3 mL) was added and the reaction mixture was purified by preparative reversed-phase preparative HPLC using a Phenomenex Gemini column, 10 µm, C18, 110 Å, 100 x 50 mm, 0.1% TFA in CH_3CN/H_2O, gradient 10% to 100% over 20 min. The desired fractions were combined and the solvent was removed under reduced pressure to obtain 92 mg of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(3-pyridazinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide as a tan solid. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.03 (d, *J*=6.06 Hz, 3 H) 1.35 (d, *J*=6.65 Hz, 3 H) 1.72 - 1.87 (m, 2 H) 1.89 - 2.23 (m, 9 H) 2.73 - 2.84 (m, 3 H) 2.94 - 3.06 (m, 2 H) 3.11 (s, 3 H) 3.26 (d, *J*=14.48 Hz, 1 H) 3.68 (d, *J*=7.04 Hz, 1 H) 3.75 (d, *J*=14.48 Hz, 1 H) 4.04 - 4.14 (m, 2 H) 4.32 (d, *J*=15.06 Hz, 1 H) 5.43 (br. s., 9 H) 5.91 (d, *J*=16.24 Hz, 1 H) 6.85 - 6.92 (m, 2 H) 7.03 (s, 1 H) 7.09 (s, 1 H) 7.16 - 7.21 (m, 1 H) 7.18 (d, *J*=8.61 Hz, 1 H) 7.70 (d, *J*=8.41 Hz, 1 H) 8.18 (br. s., 2 H) 9.48 (br. s., 1 H). MS (ESI, +ve ion) *m/z* 691.0 $(M+H)^+$.

Example 100005

2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-*N*-(2-methoxyethyl)-*N*-methylacetamide



Step 1: 2-methyl-2-propanyl ((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetate and 2-methyl-2-propanyl ((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetate

2-*tert*-Butoxy-2-oxoethylzinc chloride (0.5 M in diethyl ether, 48.6 mL, 24.28 mmol) was added to a stirred solution of (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,7'H,15'H-spiro[naphthalene-1,22'-

[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7',15'-dione 13',13'-dioxide (2.90 g, 4.86 mmol) in tetrahydrofuran (50 mL) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (150 mL) and extracted with EtOAc (100 mL). The organic layer was separated, washed with 9:1 saturated aqueous NH_4Cl:30% aqueous NH_4OH (200 mL), washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to provide a crude mixture of 2-methyl-2-propanyl ((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetate and 2-methyl-2-propanyl ((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetate that was azeotroped twice with toluene and used directly in the next step. MS (ESI, +ve) *m/z* 713.3 $[M + H]^+$.

Step 2: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(2-hydroxyethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide and (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(2-hydroxyethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

Lithium borohydride (2.0 M solution in tetrahydrofuran, 10.41 mL, 20.82 mmol) was added to a stirred solution of the crude mixture of 2-methyl-2-propanyl ((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-

[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetate and 2-methyl-2-propanyl ((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetate in tetrahydrofuran (25 mL) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 16 h. Additional lithium borohydride (2.0 M solution in tetrahydrofuran, 5.21 mL, 10.4 mmol) was added, followed by dropwise addition of methanol (1.69 mL, 41.6 mmol). The reaction mixture was stirred at room temperature for 24 h. Additional methanol (1.687 mL, 41.6 mmol) was added, and the reaction mixture was stirred for another 2.5 h. The reaction mixture was slowly quenched with saturated aqueous NH_4Cl (75 mL) and extracted twice with EtOAc (75 mL). The combined organic layers were separated, washed with brine (60 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatographic purification of the residue (silica gel, 0 to 10% MeOH in DCM) provided a mixture of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(2-hydroxyethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide and (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(2-hydroxyethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (2.58 g, 4.01 mmol, 96% yield) as a white solid. MS (ESI, +ve) *m/z* 643.2 $[M + H]^+$.

Step 3: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-((dimethyl(2-methyl-2-propanyl)silyl)oxy)ethyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

Imidazole (1.274 g, 18.72 mmol) and *tert*-butyldimethylsilyl chloride (1.41 g, 9.36 mmol) were added to a stirred mixture of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(2-hydroxyethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide and (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(2-hydroxyethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (3.01 g, 4.68 mmol) in dichloromethane (50 mL). The reaction mixture was stirred at room temperature for 72 h. Additional *tert*-butyldimethylsilyl chloride (1.41 g, 9.36 mmol) and imidazole (1.274 g, 18.72 mmol) were added, and the reaction mixture was stirred at room temperature for another 4 h. Additional reagents were added multiple times while stirring at room temperature until the reaction progressed no further upon addition. The reaction mixture was quenched with saturated aqueous NH_4Cl (125 mL) and extracted with DCM (75 mL). The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was resubjected to the original reaction conditions and stirred at room temperature for 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (125 mL) and extracted with DCM (75 mL). The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatographic purification of the residue (silica gel, 0 to 50% EtOAc in heptane) provided (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-((dimethyl(2-methyl-2-propanyl)silyl)oxy)ethyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (453 mg, 0.598 mmol, 13% yield), the second diastereomer to elute from the column, as a white solid. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.99 (1 H, s) 7.69 (1 H, d, *J*=8.41 Hz) 7.18 (1 H, dd, *J*=8.51, 2.25 Hz) 7.09 (1 H, d, *J*=2.15 Hz) 6.92 - 6.96 (3 H, m) 5.71 - 5.78 (1 H,

m) 5.59 (1 H, d, *J*=16.04 Hz) 4.55 (1 H, br. s.) 3.96 - 4.19 (5 H, m) 3.67 - 3.82 (2 H, m) 3.25 (1 H, d, *J*=14.28 Hz) 3.02 (1 H, dd, *J*=15.16, 10.27 Hz) 2.68 - 2.86 (2 H, m) 2.35 - 2.47 (1 H, m) 2.26 - 2.36 (1 H, m) 2.12 - 2.24 (3 H, m) 1.77 - 2.08 (6 H, m) 1.65 - 1.77 (1 H, m) 1.51 - 1.62 (1 H, m) 1.46 (3 H, d, *J*=7.04 Hz) 1.36 - 1.45 (1 H, m) 1.25 - 1.32 (1 H, m) 1.07 (3 H, d, *J*=6.06 Hz) 0.91 (9 H, s) 0.10 (6 H, d, *J*=3.33 Hz). MS (ESI, +ve) *m/z* 757.2 $[M + H]^+$.

Step 4: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-((dimethyl(2-methyl-2-propanyl)silyl)oxy)ethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

Sodium hydride (60% dispersion in mineral oil, 119 mg, 2.97 mmol) was added to a stirred solution of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-((dimethyl(2-methyl-2-propanyl)silyl)oxy)ethyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (225 mg, 0.297 mmol) and iodomethane (0.185 mL, 2.97 mmol) in tetrahydrofuran (2 mL). The reaction mixture was stirred at room temperature for 17 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (70 mL). The organic layer was separated, washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to provide crude (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-((dimethyl(2-methyl-2-propanyl)silyl)oxy)ethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide that was used directly in the next step. MS (ESI, +ve) *m/z* 793.3 $[M + Na]^+$.

Step 5: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-hydroxyethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-

[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

Tetrabutylammonium fluoride (1.0 M solution in tetrahydrofuran, 0.356 mL, 0.356 mmol) was added to a stirred solution of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-((dimethyl(2-methyl-2-propanyl)silyl)oxy)ethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (229 mg, 0.297 mmol) in tetrahydrofuran (1.5 mL). The reaction mixture was stirred at room temperature for 3.5 h. Additional tetrabutylammonium fluoride (1.0 M solution in tetrahydrofuran, 0.356 mL, 0.356 mmol) was added, and the reaction mixture was stirred for another 3 h. The reaction mixture was concentrated. Chromatographic purification of the residue (silica gel, 0 to 100% (EtOAc with 0.3% AcOH) in heptane) provided (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-hydroxyethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (178 mg, 0.271 mmol, 91% yield) as a white solid. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.10 (1 H, s) 7.68 (1 H, d, *J*=8.61 Hz) 7.18 (1 H, dd, *J*=8.51, 2.25 Hz) 7.09 (1 H, d, *J*=2.15 Hz) 6.88 - 6.96 (3 H, m) 5.75 - 5.83 (1 H, m) 5.64 (1 H, d, *J*=16.24 Hz) 4.29 - 4.37 (1 H, m) 4.02 - 4.15 (2 H, m) 3.91 - 3.99 (1 H, m) 3.80 - 3.88 (2 H, m) 3.72 (1 H, d, *J*=14.28 Hz) 3.25 (1 H, d, *J*=14.28 Hz) 3.11 (3 H, s) 3.02 (1 H, dd, *J*=14.96, 10.66 Hz) 2.69 - 2.85 (2 H, m) 2.59 (1 H, q, *J*=9.06 Hz) 2.34 - 2.47 (2 H, m) 2.12 - 2.24 (2 H, m) 1.76 - 2.06 (8 H, m) 1.58 - 1.67 (1 H, m) 1.50 (3 H, d, *J*=7.04 Hz) 1.38 (1 H, t, *J*=12.91 Hz) 1.06 (3 H, d, *J*=6.85 Hz). MS (ESI, +ve) *m/z* 657.2 $[M + H]^+$.

Step 6: ((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetaldehyde

Dess-Martin periodinane (67.4 mg, 0.159 mmol) was added to a stirred mixture of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-hydroxyethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (87 mg, 0.13 mmol) and sodium bicarbonate (111 mg, 1.32 mmol) in dichloromethane (1 mL). The reaction mixture was stirred at room temperature for 45 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (25 mL) and extracted with EtOAc (30 mL). The organic layer was separated, washed with 1 M aqueous $Na_2S_2O_3$ (20 mL), washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to provide crude ((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetaldehyde that was used directly in the next step.

Step 7: ((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetic acid

A solution of potassium phosphate monobasic (361 mg, 2.66 mmol) and sodium chlorite (240 mg, 2.66 mmol) in water (2 mL) was added to a stirred mixture of ((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetaldehyde (174 mg, 0.266 mmol) and 2-methyl-2-butene (1.407 mL, 13.28 mmol) in *tert*-butanol (2 mL). The reaction mixture was stirred at room temperature for 45 min. The reaction mixture was diluted with EtOAc (50 mL), washed with 1 M aqueous HCl (40 mL), washed with 1 M $Na_2S_2O_3$ (40 mL), washed with brine (40 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatographic purification of the residue (silica gel, 0 to 100% (EtOAc

with 0.3% AcOH) in heptane) provided ((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetic acid (142 mg, 0.212 mmol, 80% yield) as a white solid. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.11 (1 H, s) 7.68 (1 H, d, *J*=8.41 Hz) 7.17 (1 H, d, *J*=8.41 Hz) 7.08 (1 H, s) 6.87 - 6.95 (3 H, m) 5.80 - 5.90 (1 H, m) 5.72 (1 H, d, *J*=15.85 Hz) 4.36 (1 H, q, *J*=7.17 Hz) 4.07 (2 H, s) 3.99 (1 H, d, *J*=15.65 Hz) 3.71 (1 H, d, *J*=14.48 Hz) 3.16 - 3.27 (5 H, m) 3.01 (1 H, dd, *J*=15.55, 10.86 Hz) 2.71 - 2.84 (3 H, m) 2.66 (1 H, q, *J*=9.00 Hz) 2.42 (1 H, quin, *J*=9.15 Hz) 2.12 - 2.26 (2 H, m) 2.01 - 2.09 (1 H, m) 1.83 - 2.01 (5 H, m) 1.79 (1 H, d, *J*=7.24 Hz) 1.57 - 1.69 (1 H, m) 1.51 (3 H, d, *J*=7.04 Hz) 1.35 (1 H, t, *J*=13.11 Hz) 1.06 (3 H, d, *J*=6.65 Hz). MS (ESI, +ve) *m/z* 671.2 $[M + H]^+$.

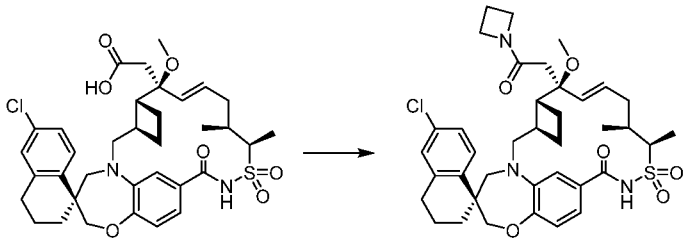
Step 8: 2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-*N*-(2-methoxyethyl)-*N*-methylacetamide

((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetic acid (28 mg, 0.042 mmol) was taken up in THF (0.5 mL) and lithium hydroxide (2.0 M in water, 0.083 mL, 0.17 mmol) was added. The mixture was stirred at room temperature for 10 min before being concentrated in vacuo to provide the lithium carboxylate of the starting material as an off-white solid that was used in the amide coupling. HATU (31.7 mg, 0.083 mmol) and *N*-(2-methoxyethyl)methylamine (0.022 mL, 0.21 mmol) were added to a stirred suspension of the lithium carboxylate previously prepared in *N*,*N*-dimethylformamide (0.50 mL). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (30 mL). The organic layer was

separated, washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatographic purification of the residue (silica gel, 0 to 100% (EtOAc with 0.3% AcOH) in heptane) followed by chromatographic purification (silica gel, 0 to 100% EtOAc in heptane) provided 2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-*N*-(2-methoxyethyl)-*N*-methylacetamide (23 mg, 0.031 mmol, 74% yield) as a white solid. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.27 (0.4 H, s) 8.10 (0.6 H, s) 7.69 (1 H, d, J=8.61 Hz) 7.17 (1 H, dd, J=8.41, 2.15 Hz) 7.08 (1 H, d, J=1.96 Hz) 6.90 - 7.06 (3 H, m) 5.84 - 5.90 (1 H, m) 5.72 - 5.83 (1 H, m) 4.28 (0.6 H, q, J=7.04 Hz) 4.19 (0.4 H, q, J=7.04 Hz) 4.05 (1.2 H, s) 4.04 (0.8 H, s) 3.95 (0.4 H, d, J=10.17 Hz) 3.91 (0.6 H, d, J=10.17 Hz) 3.52 - 3.77 (4 H, m) 3.22 - 3.34 (7 H, m) 2.97 - 3.19 (6 H, m) 2.57 - 2.82 (4 H, m) 2.38 - 2.54 (1 H, m) 1.99 - 2.23 (4 H, m) 1.72 - 1.99 (5 H, m) 1.57 - 1.68 (1 H, m) 1.46 - 1.51 (3 H, m) 1.27 - 1.37 (1 H, m) 1.04 - 1.11 (3 H, m). MS (ESI, +ve) *m/z* 742.2 [M + H]$^+$.

Example 100006

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-7'-(2-(1-azetidinyl)-2-oxoethyl)-6-chloro-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

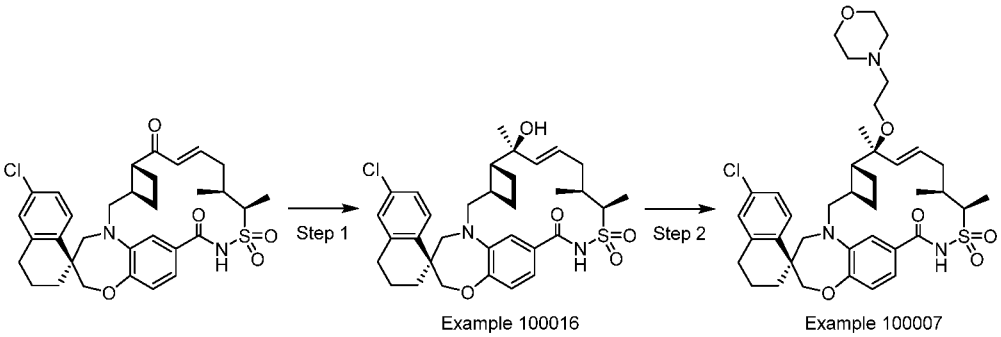


Example 100307 Example 100006

((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetic acid (28 mg, 0.042 mmol) was taken up in THF (0.5 mL) and lithium hydroxide (2.0 M in water, 0.083 mL, 0.17 mmol) was added. The mixture was stirred at room temperature for 10 min before being concentrated in vacuo to provide the lithium carboxylate of the starting material as an off-white solid that was used in the amide coupling. HATU (31.7 mg, 0.083 mmol) and azetidine (0.014 mL, 0.209 mmol) were added to a stirred suspension of the lithium carboxylate previously prepared in *N*,*N*-dimethylformamide (0.25 mL). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (15 mL). The organic layer was separated, washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatographic purification of the residue (silica gel, 0 to 100% (EtOAc with 0.3% AcOH) in heptane) followed by chromatographic purification (silica gel, 0 to 100% EtOAc in heptane) provided (1S,3'R,6'R,7'S,8'E,11'S,12'R)-7'-(2-(1-azetidinyl)-2-oxoethyl)-6-chloro-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (22 mg, 0.031 mmol, 74% yield) as a white solid. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.21 (1 H, br s) 7.68 (1 H, d, J=8.61 Hz) 7.13 - 7.20 (1 H, m) 7.06 - 7.09 (1 H, m) 6.88 - 6.97 (3 H, m) 5.70 - 5.86 (2 H, m) 4.23 - 4.39 (3 H, m) 3.98 - 4.11 (5 H, m) 3.70 (1 H, d, J=14.28 Hz) 3.22 - 3.32 (2 H, m) 3.08 - 3.18 (4 H, m) 2.81 - 2.88 (1 H, m) 2.67 - 2.79 (2 H, m) 2.33 - 2.46 (2 H, m) 2.19 - 2.31 (2 H, m) 1.72 - 2.19 (9 H, m) 1.56 - 1.69 (1 H, m) 1.49 (3 H, d, J=6.85 Hz) 1.25 - 1.36 (1 H, m) 1.06 (3 H, d, J=6.65 Hz). MS (ESI, +ve) *m/z* 710.2 $[M + H]^+$.

Example 100007 and Example 100016

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7',11',12'-trimethyl-7'-(2-(4-morpholinyl)ethoxy)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (Example 100007) and (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (Example 100016)



Step 1: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

Lanthanum(III) chloride bis(lithium chloride) complex (0.5 M solution in THF, 0.616 mL, 0.308 mmol) was added to a stirred solution of (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,7'H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7',15'-dione 13',13'-dioxide (184 mg, 0.308 mmol) in tetrahydrofuran (3 mL) at 0 °C. The mixture was stirred at 0 °C for 45 min before methylmagnesium bromide (3.0 M solution in diethyl ether, 0.462 mL, 1.39 mmol) was added dropwise via syringe. The reaction mixture was allowed to warm to room temperature and stirred for 18 h. The reaction mixture was

quenched with saturated aqueous NH_4Cl (30 mL) and extracted with EtOAc (45 mL). The organic layer was separated, washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatographic purification of the residue (silica gel, 0 to 75% (EtOAc with 0.3% AcOH) in heptane) provided (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (92 mg, 0.150 mmol, 49% yield), the second diasteromer to elute from the column, as a white solid. ^{1}H NMR (400MHz, DICHLOROMETHANE-d_2) δ 7.71 (d, *J*=8.6 Hz, 1H), 7.18 (dd, *J*=2.2, 8.5 Hz, 1H), 7.10 (d, *J*=2.2 Hz, 1H), 7.00 - 6.89 (m, 3H), 5.90 - 5.76 (m, 2H), 4.35 - 4.24 (m, 1H), 4.11 - 4.04 (m, 2H), 3.84 (br d, *J*=14.9 Hz, 1H), 3.73 (d, *J*=14.3 Hz, 1H), 3.28 (d, *J*=14.3 Hz, 1H), 3.05 (dd, *J*=10.4, 15.3 Hz, 1H), 2.86 - 2.70 (m, 2H), 2.46 - 2.33 (m, 1H), 2.27 (q, *J*=9.3 Hz, 1H), 2.18 - 2.10 (m, 1H), 2.07 (br d, *J*=2.5 Hz, 1H), 2.05 - 2.01 (m, 2H), 2.02 - 1.91 (m, 3H), 1.89 - 1.78 (m, 3H), 1.69 - 1.60 (m, 1H), 1.52 (s, 3H), 1.47 (d, *J*=7.2 Hz, 3H), 1.44 - 1.36 (m, 1H), 1.04 (d, *J*=6.8 Hz, 3H). MS (ESI, +ve) *m/z* 613.3 $[M + H]^+$.

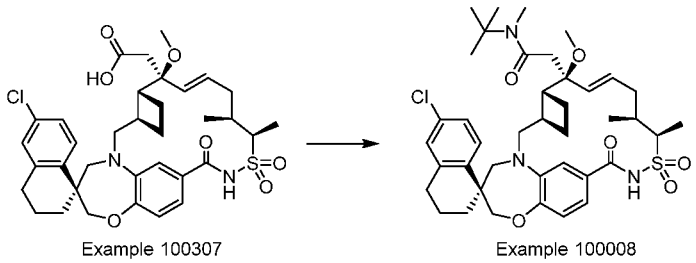
Step 2: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7',11',12'-trimethyl-7'-(2-(4-morpholinyl)ethoxy)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (33 mg, 0.054 mmol), 4-(2-bromoethyl)morpholine hydrobromide (296 mg, 1.08 mmol), and sodium hydride (60% dispersion in mineral oil, 86 mg, 2.2 mmol) were mixed in *N*,*N*-dimethylformamide (1.5 mL). The reaction mixture was stirred at room temperature for 20 h. The reaction mixture was quenched with saturated aqueous

NH_4Cl (20 mL) and extracted two times with EtOAc (30 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatographic purification of the residue (silica gel, 50% to 100% EtOAc in DCM until the starting material eluted and then 0 to 10% (2 M NH_3 in MeOH) in DCM) provided (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7',11',12'-trimethyl-7'-(2-(4-morpholinyl)ethoxy)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (25 mg, 0.034 mmol, 64% yield) as an off-white solid. ^1H NMR (400 MHz, CHLOROFORM-*d*) δ 7.68 (1 H, d, J=8.41 Hz) 7.17 (1 H, dd, J=8.41, 2.15 Hz) 7.08 (1 H, d, J=2.15 Hz) 6.89 - 6.96 (3 H, m) 5.82 (1 H, ddd, J=15.85, 9.59, 2.74 Hz) 5.65 (1 H, d, J=15.85 Hz) 4.29 (1 H, q, J=7.11 Hz) 4.00 - 4.11 (2 H, m) 3.83 (1 H, d, J=14.67 Hz) 3.68 - 3.77 (5 H, m) 3.33 - 3.46 (2 H, m) 3.26 (1 H, d, J=14.28 Hz) 3.00 (1 H, dd, J=15.16, 10.66 Hz) 2.69 - 2.84 (2 H, m) 2.52 - 2.61 (6 H, m) 2.40 (1 H, quin, J=8.95 Hz) 2.28 (1 H, q, J=9.13 Hz) 1.74 - 2.21 (9 H, m) 1.52 - 1.64 (1 H, m) 1.48 (3 H, d, J=7.04 Hz) 1.33 - 1.43 (4 H, m) 1.04 (3 H, d, J=6.85 Hz). MS (ESI, +ve) *m/z* 726.3 $[M + H]^+$.

Example 100008

2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N-methyl-N-(2-methyl-2-propanyl)acetamide



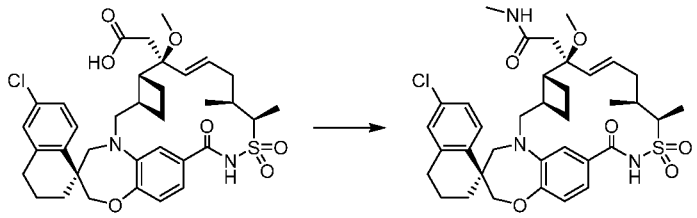
Example 100307 Example 100008

A drop of DMF was added to a stirred solution of oxalyl chloride (10 μL, 0.11 mmol) and ((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetic acid (37 mg, 0.055 mmol) in dichloromethane (1 mL). The reaction mixture was stirred at room temperature for 20 min before being concentrated in vacuo. The resulting yellow residue was taken up in dichloromethane (1 mL) and *N*-*tert*-butylmethylamine (0.066 mL, 0.55 mmol) was added. The reaction mixture was stirred at room temperature for 40 min. The reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (30 mL). The organic layer was separated, washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatographic purification of the residue (silica gel, 0 to 50% (EtOAc with 0.3% AcOH) in heptane) provided 2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N-methyl-N-(2-methyl-2-propanyl)acetamide (18 mg, 0.024 mmol, 44% yield) as an off-white solid. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ 8.01 (1 H, s) 7.68 (1 H, d, J=8.41 Hz) 7.17 (1 H, dd, J=8.51, 2.25 Hz) 7.08 (1 H, d, J=1.96 Hz) 6.88 - 6.96 (3 H, m) 5.68 - 5.81 (2 H, m) 4.33 (1 H, q, J=7.43 Hz) 4.07 (2 H, s) 3.85 (1 H, d, J=15.06 Hz) 3.71 (1 H, d, J=14.28 Hz) 3.22 - 3.36 (2 H, m) 3.11 (3 H, s) 3.01 - 3.09 (5 H, m) 2.68 - 2.84 (2 H, m) 2.59 (1 H, d, J=15.85 Hz) 2.33 - 2.44 (1 H, m) 2.06 - 2.23 (2 H, m) 1.74 - 2.06 (7 H, m) 1.55 - 1.66 (1 H, m) 1.24 - 1.52 (13 H, m) 1.06 (3 H, d, J=6.65 Hz). MS (ESI, +ve) *m/z* 762.3 $[M + Na]^+$.

Example 100009

2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-

[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N-methylacetamide



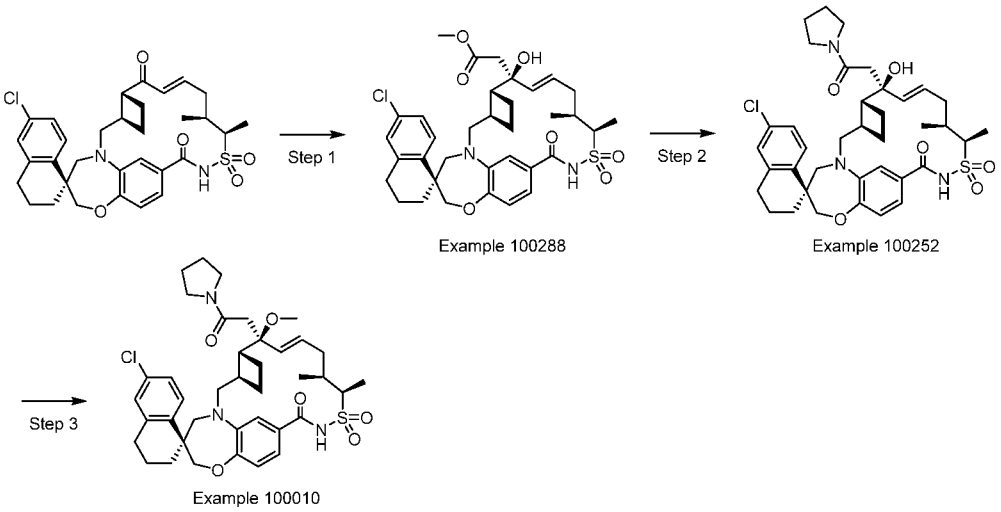
Example 100307 Example 100009

((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-Chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetic acid (50 mg, 0.074 mmol) was taken up in THF (2 mL) and lithium hydroxide (2.0 M in water, 0.149 mL, 0.358 mmol) was added. The mixture was stirred at room temperature for 10 min before being concentrated in vacuo to provide the lithium carboxylate of the starting material as an off-white solid that was used in the amide coupling. HATU (42.0 mg, 0.112 mmol) and methylamine (2.0 M in THF, 0.112 mL, 0.223 mmol) were added to a stirred suspension of the lithium carboxylate previously prepared in *N*,*N*-dimethylformamide (2 mL). The reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with water and EtOAc and transferred to a separatory funnel. 1.0 M HCl was added and the phases were mixed. The organic layer was separated and washed sequentially with 1.0 M LiCl and brine then dried over magnesium sulfate and concentrated under reduced pressure. Purification via silica gel flash chromatography using a gradient of 50% to 100% EtOAc with 0.3% AcOH in heptane afforded 2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N-methylacetamide (44 mg, 0.064 mmol, 86% yield) as a white solid. ^{1}H NMR (300 MHz, DICHLOROMETHANE-d_2) δ 7.69 - 7.79 (m, 1 H) 7.19 (br dd, *J*=8.84, 1.10 Hz, 1 H) 7.12 (s, 1 H) 6.88 - 7.03 (m, 3 H) 6.74 - 6.86

(m, 1 H) 5.75 - 5.89 (m, 1 H) 5.62 - 5.73 (m, 1 H) 4.21 - 4.36 (m, 1 H) 4.09 (s, 2 H) 3.91 - 4.04 (m, 1 H) 3.72 (br d, *J*=15.05 Hz, 1 H) 3.29 (br d, *J*=14.03 Hz, 1 H) 3.16 (s, 3 H) 2.92 - 3.09 (m, 2 H) 2.73 - 2.90 (m, 6 H) 2.51 - 2.66 (m, 2 H) 2.37 - 2.49 (m, 1 H) 1.67 - 2.25 (m, 11 H) 1.48 (br d, *J*=7.02 Hz, 3 H) 1.22 - 1.43 (m, 6 H) 1.06 (br d, *J*=6.58 Hz, 3 H). MS (ESI, +ve) *m/z* 652.0 $[M - OMe]^+$.

Example 100010

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-oxo-2-(1-pyrrolidinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide



Step 1: methyl ((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetate

A flame dried round bottom flask was charged with tetrahydrofuran (6.28 mL) and lithium diisopropylamide (2.0 M solution in heptane/tetrahydrofuran/ethylbenzene, 7.54 mL, 15.1 mmol). The solution was cooled to -78 °C then a solution of methyl acetate (1.197 mL, 15.07 mmol) in

tetrahydrofuran (6.28 mL) was added dropwise and the reaction was stirred at -78 °C for 45 minutes. The flask was equipped with an addition funnel which was then charged with a solution of (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,7'H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7',15'-dione 13',13'-dioxide (1.5 g, 2.5 mmol) in tetrahydrofuran (12.56 mL). The reaction was stirred at -78 °C for 30 minutes. The reaction was quenched with water and warmed to room temperature. The reaction was diluted with water and EtOAc and transferred to a separatory funnel. 1 M HCl was added. The phases were mixed and the organic layer was separated, washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The crude residue was purified via silica gel flash chromatography using a gradient of 20% to 70% EtOAc with 0.3% AcOH in heptane to afford methyl ((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetate (0.666 g, 0.992 mmol, 40% yield), the second eluting diastereomer, as a white solid. ^{1}H NMR (300 MHz, DICHLOROMETHANE-d_2) δ 8.06 - 8.25 (m, 1 H) 7.74 (d, *J*=8.62 Hz, 1 H) 7.20 (br d, *J*=8.77 Hz, 1 H) 7.13 (s, 1 H) 6.96 (s, 2 H) 6.92 (s, 1 H) 5.64 - 5.81 (m, 2 H) 4.06 - 4.25 (m, 3 H) 3.80 (s, 3 H) 3.75 (br d, *J*=14.03 Hz, 1 H) 3.70 (s, 1 H) 3.31 (d, *J*=14.18 Hz, 1 H) 3.00 - 3.11 (m, 1 H) 2.91 - 3.00 (m, 1 H) 2.69 - 2.87 (m, 3 H) 2.32 - 2.56 (m, 2 H) 1.79 - 2.21 (m, 9 H) 1.59 - 1.71 (m, 2 H) 1.46 (d, *J*=7.16 Hz, 4 H) 1.34 - 1.39 (m, 4 H) 1.06 (d, *J*=6.58 Hz, 3 H). MS (ESI, +ve) *m/z* 671.2 $[M + H]^+$.

Step 2: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-oxo-2-(1-pyrrolidinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

To a solution of methyl ((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetate (0.343 g, 0.511 mmol) in THF (10.22 mL) was added lithium hydroxide (2.0 M in water, 0.639 mL, 1.28 mmol). The reaction was stirred at room temperature overnight. The reaction was concentrated under reduced pressure and used without further purification. To a suspension of the lithium carboxylate previously generated in DMF (2.5 mL) was added HATU (0.069 g, 0.18 mmol) followed by pyrrolidine (0.050 mL, 0.60 mmol). The reaction was stirred at room temperature for 30 minutes. The reaction was diluted with water and EtOAc and transferred to a separatory funnel. 1.0 M HCl was added and the phases were mixed. The organic layer was separated then washed sequentially with 1.0 M LiCl and brine then dried over magnesium sulfate and concentrated under reduced pressure. Purification via silica gel flash chromatography using a gradient of 75% to 100% EtOAc with 0.3% AcOH in heptane afforded (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-oxo-2-(1-pyrrolidinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (0.0608 g, 0.086 mmol, 71% yield) as a white solid. MS (ESI, +ve) *m/z* 710.3 $[M + H]^+$.

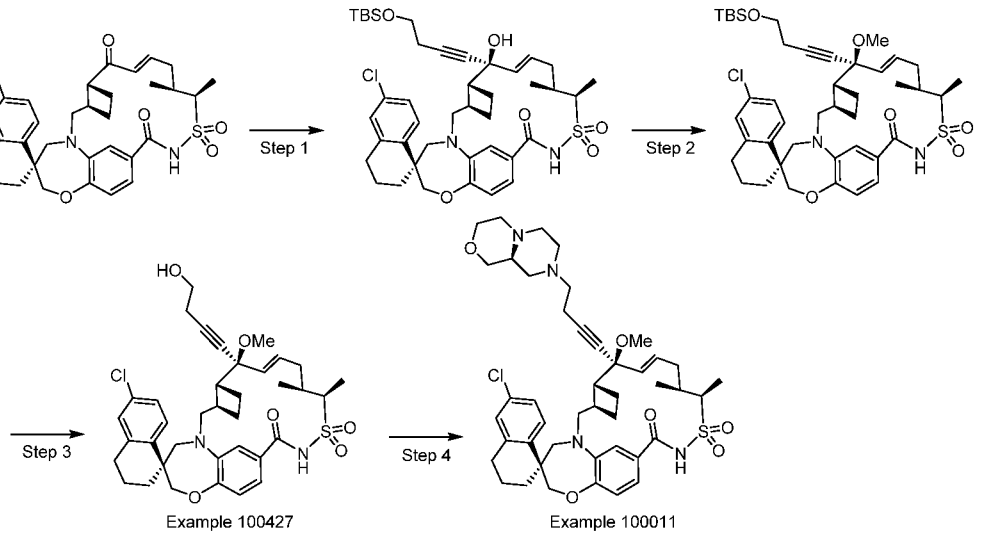
Step 3: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-oxo-2-(1-pyrrolidinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

A solution of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-oxo-2-(1-pyrrolidinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-

[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (0.0608 g, 0.086 mmol) in THF (0.856 mL) was cooled to 0 °C before adding sodium hydride (0.017 g, 0.428 mmol). The reaction was stirred for 30 minutes then iodomethane (0.053 mL, 0.856 mmol) was added and the reaction was warmed to room temperature and stirred for 1 hour. A larger portion of iodomethane (0.150 mL) was added and the reaction was allowed to stir at room temperature overnight. An additional portion of MeI (0.15 mL) was added and the reaction was continued at room temperature for 6 h. The reaction was quenched with water and diluted with water and EtOAc. The reaction was transferred to a separatory funnel and 1 M HCl was added. The phases were mixed and the organic layer was separated, washed with brine and dried over magnesium sulfate. The crude material was purified via silica gel flash chromatography using 100% EtOAc with 0.6% AcOH. The reaction was repeated a second time on the same scale and the material from both reactions was combined and further purified by preparative supercritical fluid chromatography SFC using the following conditions: Diol Column (21.2 x 250 mm, 5 μm); 20% MeOH with 20 mM NH_3 in CO_2 to afford (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-oxo-2-(1-pyrrolidinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (0.018 g, 0.025 mmol, 15% yield) as a white solid. ^{1}H NMR (300 MHz, DICHLOROMETHANE-d_2) δ 7.75 (br d, J=8.18 Hz, 1 H) 7.20 (br d, J=8.48 Hz, 1 H) 7.12 (br s, 2 H) 7.00 - 7.06 (m, 1 H) 6.90 - 6.98 (m, 1 H) 5.75 - 5.99 (m, 2 H) 4.13 - 4.24 (m, 1 H) 4.10 (s, 2 H) 3.86 - 3.96 (m, 1 H) 3.74 (br d, J=14.32 Hz, 1 H) 3.57 - 3.68 (m, 2 H) 3.41 - 3.54 (m, 2 H) 3.34 (br d, J=14.62 Hz, 1 H) 3.07 - 3.25 (m, 4 H) 3.03 (br d, J=15.93 Hz, 1 H) 2.69 - 2.92 (m, 2 H) 2.46 - 2.67 (m, 2 H) 2.04 - 2.26 (m, 4 H) 1.74 - 2.03 (m, 9 H) 1.49 - 1.73 (m, 9 H) 1.46 (br d, J=6.72 Hz, 3 H) 1.29 - 1.41 (m, 2 H) 1.03 - 1.14 (m, 3 H). MS (ESI, +ve) m/z 692.2 $[M - OMe]^+$.

Example 100011

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(4-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-1-butyn-1-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide



Step 1: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(4-((dimethyl(2-methyl-2-propanyl)silyl)oxy)-1-butyn-1-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

To a cooled (-78 °C) solution of 4-(tert-butyldimethylsilyl)-1-butyne (2.50 mL, 12.1 mmol) in tetrahydrofuran (30 mL) was added 2.5 M butyllithium in toluene (4.0 mL, 10 mmol) dropwise via syringe over a period of 15 min. After 1 h, a solution of (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,7'H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7',15'-dione 13',13'-dioxide (1.008 g, 1.688 mmol) in THF (10 mL) was added dropwise and stirred for 1 h. The reaction was quenched with pH 7 buffer (10 mL) and warmed to room temperature. The aqueous layer was

extracted with EtOAc (3x). The combined organic layers were washed with brine and dried over Na_2SO_4. The solution was filtered, evaporated onto silica gel and purified by flash chromatography (Isco, 40 g) eluting with 0.3% AcOH in EtOAc : 0.3% AcOH in heptane (0:1 to 1:3) to give (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(4-((dimethyl(2-methyl-2-propanyl)silyl)oxy)-1-butyn-1-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (468 mg, 36% yield) as a white solid. MS (ESI, +ve ion) *m/z* 763.4 $(M+1)^+$.

Step 2: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(4-((dimethyl(2-methyl-2-propanyl)silyl)oxy)-1-butyn-1-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

To a cooled (0 °C) solution of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(4-((dimethyl(2-methyl-2-propanyl)silyl)oxy)-1-butyn-1-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (0.510 g, 0.653 mmol) in tetrahydrofuran (10 mL) was added 60% sodium hydride in mineral oil (0.211 g, 5.28 mmol) in portions. After 15 min iodomethane (0.160 mL, 2.58 mmol) was added and the reaction was allowed to warm to room temperature overnight. The reaction mixture was quenched with pH 7 buffer and partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc (3x) then the combined organic layers were washed with brine, evaporated onto silica gel and purified by flash chromatography (Isco, 25 g) eluting with 0.3% AcOH in EtOAc : 0.3% AcOH in heptane (0:1 to 1:3) to give (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(4-((dimethyl(2-methyl-2-propanyl)silyl)oxy)-1-butyn-1-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,2

4]tetraen]-15'-one 13',13'-dioxide (368 mg, 71% yield) as a white solid. MS (ESI, +ve ion) *m/z* 795.4 $(M+1)^+$.

Step 3: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(4-hydroxy-1-butyn-1-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

To a room temperature solution of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(4-((dimethyl(2-methyl-2-propanyl)silyl)oxy)-1-butyn-1-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (0.365 g, 0.459 mmol) in tetrahydrofuran (5 mL) was added 1 M tetrabutylammonium fluoride in tetrahydrofuran (1.5 mL, 1.5 mmol) via syringe. The reaction was evaporated onto silica gel and purified by flash chromatography (Isco (12 gram HP)) eluting with 0.3% AcOH in EtOAc : 0.3% AcOH in heptane (0:1 to 1:1) to give (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(4-hydroxy-1-butyn-1-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (279 mg, 89% yield) as a white solid. MS (ESI, +ve ion) *m/z* 681.3 $(M+1)^+$.

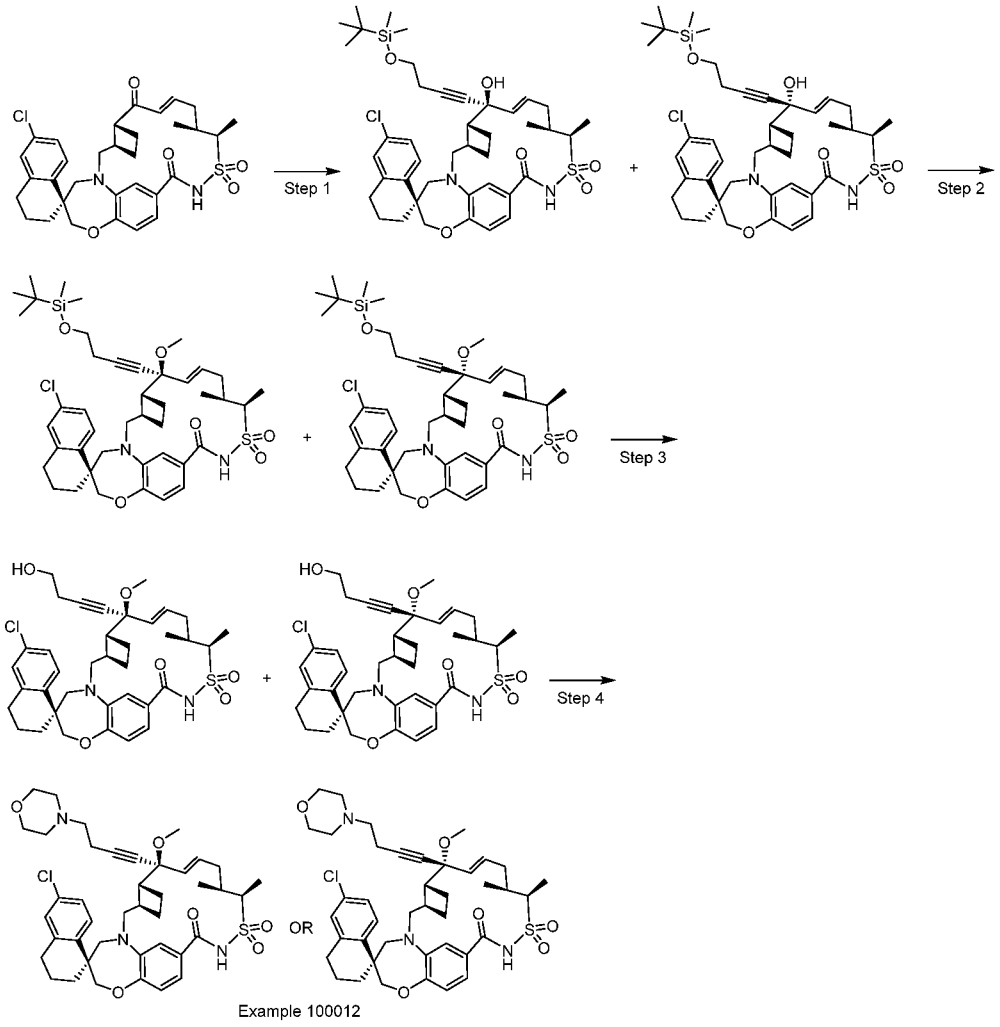
Step 4: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(4-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-1-butyn-1-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

To a cooled (0 °C) solution of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(4-hydroxy-1-butyn-1-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,2

4]tetraen]-15'-one 13',13'-dioxide (0.023 g, 0.034 mmol) in dichloromethane (1 mL) was added triethylamine (0.020 mL, 0.14 mmol) followed by methanesulfonyl chloride (0.015 mL, 0.19 mmol) and the reaction was stirred for 20 min. To the reaction was added a slurry of (S)-octahydropyrazino[2,1-c]morpholine dihydrochloride (0.067 g, 0.31 mmol) and triethylamine in dichloromethane (1 mL) and the reaction was stirred at room temperature for 85 h and at 45 °C for 4 h. The reaction was cooled to room temperature, diluted with DCM, evaporated onto silica gel and purified by flash chromatography (Isco, 4 g) eluting with 25% EtOH/EtOAc : heptane (0:1 to 1:0) to give (12.6 mg, 46% yield) light-yellow solid. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.72 (d, *J*=8.41 Hz, 1 H), 7.20 (s, 1 H), 7.17 (dd, *J*=8.51, 2.05 Hz, 1 H), 7.09 (d, *J*=2.15 Hz, 1 H), 6.85 - 6.98 (m, 2 H), 6.20 - 6.39 (m, 1 H), 5.52 (d, *J*=15.84 Hz, 1 H), 4.32 (d, *J*=15.65 Hz, 1 H), 4.26 (d, *J*=6.46 Hz, 1 H), 4.14 (d, *J*=12.13 Hz, 1 H), 4.00 - 4.11 (m, 2 H), 3.75 (dd, *J*=11.15, 2.93 Hz, 1 H), 3.69 (d, *J*=14.08 Hz, 1 H), 3.51 - 3.64 (m, 2 H), 3.27 (d, *J*=14.28 Hz, 1 H), 3.07 - 3.19 (m, 4 H), 3.01 (dd, *J*=15.26, 10.37 Hz, 1 H), 2.87 (d, *J*=7.43 Hz, 1 H), 2.74 - 2.83 (m, 3 H), 2.50 - 2.72 (m, 8 H), 2.37 - 2.49 (m, 1 H), 2.08 - 2.27 (m, 7 H), 1.77 - 1.99 (m, 5 H), 1.57 - 1.75 (m, 2 H), 1.34 - 1.51 (m, 4 H), 1.03 (d, *J*=6.85 Hz, 3 H). MS (ESI, +ve ion) *m/z* 805.3 $(M+1)^+$.

Example 100012

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(4-(4-morpholinyl)-1-butyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(4-(4-morpholinyl)-1-butyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide



Example 100012

Step 1: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(4-((dimethyl(2-methyl-2-propanyl)silyl)oxy)-1-butyn-1-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(4-((dimethyl(2-methyl-2-propanyl)silyl)oxy)-1-butyn-1-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

To a cooled (-78 °C) solution of 4-(tert-butyldimethylsilyloxy)-1-butyne (0.600 mL, 2.91 mmol) in tetrahydrofuran (9 mL) was added 2.5 M butyllithium solution in toluene (1.00 mL, 2.50 mmol) dropwise over a period of 10 min. After 1 h, a solution of (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,7'H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7',15'-dione 13',13'-dioxide (0.249 g, 0.417 mmol) in THF (2 mL) was added dropwise via syringe. After 1 h the reaction mixture was quenched with pH 7 buffer, partitioned between EtOAc and brine and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were evaporated onto silica gel and purified by flash chromatography (Isco, 12 g) eluting with 0.3% AcOH in EtOAc : 0.3% AcOH in heptane (0:1 to 1:3) to give (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(4-((dimethyl(2-methyl-2-propanyl)silyl)oxy)-1-butyn-1-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(4-((dimethyl(2-methyl-2-propanyl)silyl)oxy)-1-butyn-1-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (254 mg, 78% yield) as a white solid. MS (ESI, +ve ion) *m/z* 784.5 $(M+1)^+$.

Step 2: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(4-((dimethyl(2-methyl-2-propanyl)silyl)oxy)-1-butyn-1-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(4-((dimethyl(2-methyl-2-propanyl)silyl)oxy)-1-butyn-1-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-

[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

To a cooled (0 °C) solution of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(4-((dimethyl(2-methyl-2-propanyl)silyl)oxy)-1-butyn-1-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(4-((dimethyl(2-methyl-2-propanyl)silyl)oxy)-1-butyn-1-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (0.254 g, 0.325 mmol) in tetrahydrofuran (5 mL) was added 60% NaH in mineral oil (0.105 g, 2.63 mmol) portion wise. After 10 min iodomethane (0.080 mL, 1.3 mmol) was added via syringe and the reaction was allowed to warm to room temperature overnight. The reaction mixture was quenched with pH 7 buffer and partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc (3x) then the combined organic layers were washed with brine, evaporated onto silica gel and purified by flash chromatography (Isco, 25 g) eluting with 0.3% AcOH in EtOAc : 0.3% AcOH in heptane (0:1 to 1:3) to give (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(4-((dimethyl(2-methyl-2-propanyl)silyl)oxy)-1-butyn-1-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(4-((dimethyl(2-methyl-2-propanyl)silyl)oxy)-1-butyn-1-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (173 mg, 67% yield) as a white solid. MS (ESI, +ve ion) *m/z* 796.3 $(M+1)^+$.

Step 3: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(4-hydroxy-1-butyn-1-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-

[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(4-hydroxy-1-butyn-1-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

To a room temperature solution of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(4-((dimethyl(2-methyl-2-propanyl)silyl)oxy)-1-butyn-1-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(4-((dimethyl(2-methyl-2-propanyl)silyl)oxy)-1-butyn-1-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (0.173 g, 0.217 mmol) in tetrahydrofuran (3 mL) was added 1 M tetrabutylammonium fluoride solution in THF (0.700 mL, 0.700 mmol). The reaction was partitioned between EtOAc and brine and the organic layer was evaporated onto silica gel and purified by flash chromatography (Isco (12 gram)) eluting with 25% EtOH/EtOAc:heptane (0:1 to 1:0) to give (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(4-hydroxy-1-butyn-1-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(4-hydroxy-1-butyn-1-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (91 mg, 61% yield) as a white solid.

Step 4: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(4-(4-morpholinyl)-1-butyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-

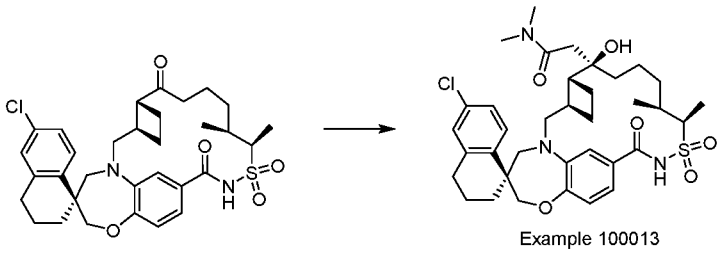
[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(4-(4-morpholinyl)-1-butyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide

To a cooled (0 °C) solution of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(4-hydroxy-1-butyn-1-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(4-hydroxy-1-butyn-1-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (0.057 g, 0.084 mmol) in dichloromethane (1.5 mL) was added triethylamine (0.060 mL, 0.43 mmol) followed by methanesulfonyl chloride (0.035 mL, 0.45 mmol) resulting in a yellow mixture. After 15 min morpholine (0.075 mL, 0.86 mmol) was added the reaction was stirred for 1 h. To the reaction was added morpholine (0.035 mL) and the reaction was stirred at room temperature overnight. The reaction mixture was partitioned between CH_2Cl_2 and brine and the aqueous layer was extracted with CH_2Cl_2 and brine (2x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 110 mg of a yellow tar. The material was purified following a 2-step SFC method: (Step 1: Cyano column, 20% isopropanol/20 mM NH_3 80 g/min Step 2: MSA column, 40% MeOH/20 mM NH_3) to give the first eluting isomer, (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(4-(4-morpholinyl)-1-butyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-

methoxy-11',12'-dimethyl-7'-(4-(4-morpholinyl)-1-butyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (6 mg, 10% yield) as a white crystalline solid. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.72 (d, *J*=8.41 Hz, 1 H), 7.19 (s, 1 H), 7.17 (dd, *J*=8.51, 2.25 Hz, 1 H), 7.09 (d, *J*=2.15 Hz, 1 H), 6.80 - 6.95 (m, 2 H), 6.23 - 6.39 (m, 1 H), 5.52 (d, *J*=15.26 Hz, 1 H), 4.39 (d, *J*=14.87 Hz, 1 H), 4.26 - 4.34 (m, 1 H), 4.01 - 4.14 (m, 2 H), 3.69 (d, *J*=14.08 Hz, 1 H), 3.58 (t, *J*=4.69 Hz, 4 H), 3.26 (d, *J*=14.28 Hz, 1 H), 3.12 (s, 3 H), 3.00 (dd, *J*=15.16, 10.47 Hz, 1 H), 2.63 - 2.86 (m, 5 H), 2.51 - 2.63 (m, 2 H), 2.51 - 2.63 (m, 2 H), 2.34 - 2.48 (m, 5 H), 2.11 - 2.24 (m, 2 H), 2.04 - 2.11 (m, 1 H), 1.75 - 2.03 (m, 6 H), 1.59 - 1.72 (m, 1 H), 1.46 (d, *J*=7.24 Hz, 3 H), 1.39 (t, *J*=13.20 Hz, 1 H), 1.03 (d, *J*=6.65 Hz, 3 H). MS (ESI, +ve ion) *m/z* 750.3 $(M+1)^+$.

Example 100013

2-((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N,N-dimethylacetamide



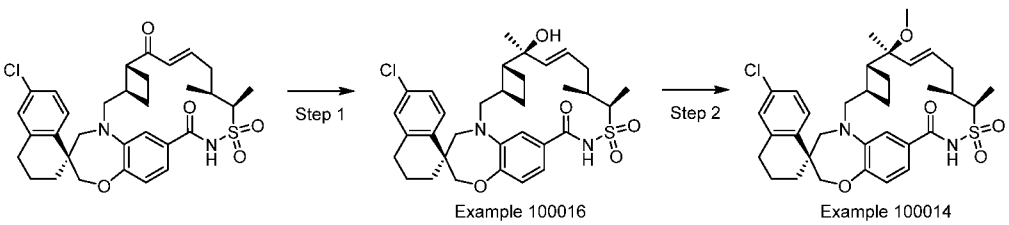
Example 100013

N-Butyllithium solution (1.6 M in hexane, 0.83 mL, 1.3 mmol) was added to a solution of diisopropylamine (0.19 mL, 1.3 mmol) in THF (1.0 mL) at 0 °C. The solution was stirred at 0 °C for 2 minutes then dimethyl acetamide (0.12 mL, 1.3 mmol) was added. The reaction was then stirred at 0 °C for 7 min. Then a solution of (1S,3'R,6'R,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,7'H,15'H-spiro[naphthalene-1,22'-

[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene]-7',15'-dione 13',13'-dioxide (0.040 g, 0.067 mmol) in THF (1.3 mL) was added and maintained at 0 °C for 17 min. The reaction was quenched with saturated ammonium chloride solution and acidified with 1 N HCl to pH 2-3 and extracted with EtOAc. The organic phase was washed with brine and dried over anhydrous sodium sulfate and the filtrate was concentrated under reduced pressure to give the crude product that was purified by preparatory SFC chromatography (CC4 250 mm x 21 mm column, Phenomenex; 33 g/minute MeOH (2 M ammonia as a modifier)+ 27 g/minute CO_2 on Thar 200 SFC; outlet pressure = 100 bar; temperature = 40 °C; wavelength = 246 nm; 2.0 mL injection of 30 mg/mL sample solution of 1:1 DCM:MeOH (2.0 mL) to give 2-((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2h-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-n,n-dimethylacetamide (17 mg, 37% yield) as the first eluting diasteromer. ^{1}H NMR (400MHz, DICHLOROMETHANE-d_2) δ 7.71 (d, *J*=8.4 Hz, 1H), 7.16 (dd, *J*=2.2, 8.5 Hz, 1H), 7.09 (d, *J*=2.2 Hz, 1H), 7.04 - 6.98 (m, 2H), 6.97 - 6.91 (m, 1H), 5.23 (br s, 1H), 4.17 - 4.06 (m, 3H), 3.68 (d, *J*=14.3 Hz, 1H), 3.58 (d, *J*=15.3 Hz, 1H), 3.23 (d, *J*=14.3 Hz, 1H), 3.17 (s, 3H), 3.02 (dd, *J*=9.7, 15.4 Hz, 1H), 2.97 (s, 3H), 2.84 - 2.67 (m, 4H), 2.65 - 2.54 (m, 1H), 2.46 (quin, *J*=9.0 Hz, 1H), 2.10 - 1.97 (m, 2H), 1.96 - 1.72 (m, 5H), 1.68 - 1.42 (m, 5H), 1.39 (d, *J*=7.2 Hz, 3H), 1.37 - 1.35 (m, 1H), 1.35 - 1.18 (m, 2H), 0.99 (d, *J*=6.7 Hz, 3H). MS (ESI, +ve ion) *m/z* 686.2 $(M+1)^+$.

Example 100014

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide



Example 100016 Example 100014

Step 1: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-CHLORO-7'-HYDROXY-7',11',12'-TRIMETHYL-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[8,16,18,24]TETRAEN]-15'-ONE 13',13'-DIOXIDE

(1S,3'R,6'R,8'E,11'S,12'R)-6-Chloro-11',12'-dimethyl-3,4-dihydro-2H,7'H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7',15'-dione 13',13'-dioxide (200 mg, 0.335 mmol) was dissolved in THF (3.00 mL) and cooled to 0 °C. Lanthanum (III) chloride bis(lithium chloride) complex solution (0.6 M in THF, 0.63 mL, 0.34 mmol) was added to the solution and the solution was stirred for 45 minutes. The methylmagnesium bromide (3.0 M in diethyl ether solution, 0.50 mL, 1.5 mmol) was added to the solution and allowed to warm to room temperature overnight. Another aliquot of methylmagnesium bromide (3.0 M in diethyl ether solution, 0.502 mL, 1.51 mmol) was added and the reaction was stirred for 30 minutes to completion then quenched with saturated ammonium chloride solution. This solution was then acidified to pH 6.5 and then extracted with EtOAc (2 x 50 mL). The combined organic layers were then washed with brine (1 x 20 mL) and dried over sodium sulfate. The residue was then purified by chromatography (silica, 20% to 100% EtOAc (0.3% HOAc) : hexanes) to give (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (124 mg, 60% yield) as the second eluting diastereomer. MS (ESI, +ve ion) *m/z* 613.1 $(M+1)^+$.

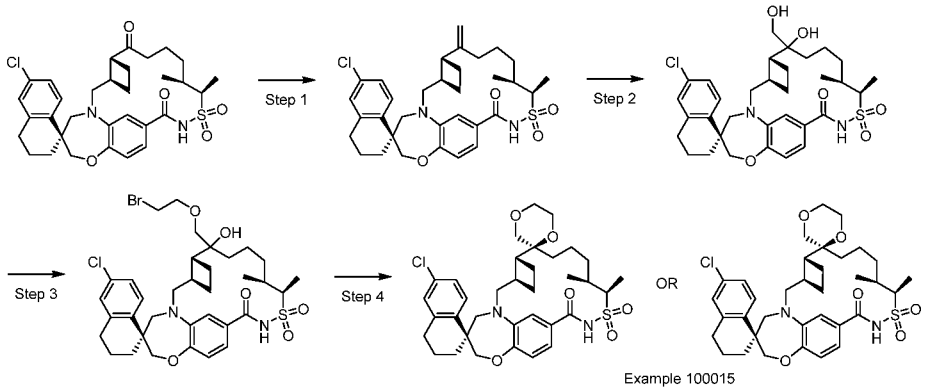
Step 2: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-CHLORO-7'-METHOXY-7',11',12'-TRIMETHYL-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[8,16,18,24]TETRAEN]-15'-ONE 13',13'-DIOXIDE.

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-Chloro-7'-hydroxy-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (30 mg, 0.049 mmol) was dissolved in tetrahydrofuran (1.0 mL) and cooled to 0 °C. Sodium hydride (60% dispersion, 20 mg, 0.49 mmol) was then added and the resulting slurry was stirred for 20 minutes. The methyl iodide (0.031 mL, 0.49 mmol) was then added and the reaction mixture was stirred for 2.5 hours while slowly warming to room temperature. Another aliquot of sodium hydride (60% dispersion, 20 mg, 0.49 mmol) and methyl iodide (0.031 mL, 0.49 mmol) was added and the reaction was stirred for an additional 3.5 h to completion. The reaction was then quenched with dropwise addition of satd. ammonium chloride addition and the mixture was extracted with EtOAc (2 x 50 mL). The combined organic layers were then washed with brine (1 x 20 mL) and dried over sodium sulfate. The crude product was purified by chromatography (silica, 0 to 50% EtOAc/hexanes) to give (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide. (29 mg, 95% yield). ^{1}H NMR (400MHz, DMSO-d_6) δ 11.89 (s, 1H), 7.64 (d, *J*=8.6 Hz, 1H), 7.27 (dd, *J*=2.1, 8.5 Hz, 1H), 7.17 (d, *J*=2.0 Hz, 1H), 7.03 (dd, *J*=1.5, 8.1 Hz, 1H), 6.89 (d, *J*=8.2 Hz, 1H), 6.79 (s, 1H), 5.72 (dd, *J*=3.2, 9.3 Hz, 1H), 5.65 - 5.55 (m, 1H), 4.16 - 4.08 (m, 1H), 4.07 - 3.94 (m, 2H), 3.69 (d, *J*=14.7 Hz, 1H), 3.59 (d, *J*=14.3 Hz, 1H), 3.24 (d, *J*=14.3 Hz, 1H), 3.08 (dd, *J*=9.6, 14.7 Hz, 1H), 2.94 (s, 3H), 2.84 - 2.62 (m, 2H),

2.36 - 1.60 (m, 12H), 1.43 - 1.36 (m, 1H), 1.33 (d, *J*=7.2 Hz, 3H), 1.30 (s, 3H), 0.96 (d, *J*=6.7 Hz, 3H). MS (ESI, +ve ion) *m/z* 627.2 $(M+1)^+$.

Example 100015

(2S,3'R,6'R,11'S,12'R,22'S)-6"-chloro-11',12'-dimethyl-3",4"-dihydro-2"H,15'H-dispiro[1,4-dioxane-2,7'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-22',1"-naphthalen]-15'-one 13',13'-dioxide OR (2R,3'R,6'R,11'S,12'R,22'S)-6"-chloro-11',12'-dimethyl-3",4"-dihydro-2"H,15'H-dispiro[1,4-dioxane-2,7'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-22',1"-naphthalen]-15'-one 13',13'-dioxide



Step 1: (1S,3'R,6'R,8'E,11'S,12'R)-6-CHLORO-11',12'-DIMETHYL-7'-METHYLIDENE-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.~3,6~.0~19,24~]PENTACOSA[8,16,18,24]TETRAEN]-15'-ONE 13',13'-DIOXIDE

A solution of methyltriphenylphosphonium bromide (1.80 g, 5.0 mmol) in THF (15 mL) was cooled to 0 °C. N-butyllithium solution (2.5 M in hexanes, 1.8 mL, 4.5 mmol) was added dropwise and the solution was stirred at 0 °C for 10 minutes. The solution was added dropwise to a solution of (1S,3'R,6'R,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,7'H,15'H-spiro[naphthalene-1,22'-

[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene]-7',15'-dione 13',13'-dioxide (0.30 g, 0.50 mmol) in THF (6.0 mL), cooled in ice bath, until the yellow color persisted. The solution was stirred at 0 °C for 12 min. The reaction mixture was added to stirred ice water (20 mL) and acidified with 1 N HCl to pH 2-4. The organic phase was separated and the aqueous was extracted with EtOAc (50 mL). The organic phase was washed with brine and dried over magnesium sulfate. The filtrate was concentrated to give crude product. The compound was purified by chromatography (silica, 0 to 50% EtOAc (0.3% HOAc:hexanes) to give (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-7'-methylidene-3,4-dihydro-2h,15'h-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (290 mg, 97% yield). MS (ESI, +ve ion) *m/z* 595.2 $(M+H)^+$.

Step 2: (1S,3'R,6'R,8'E,11'S,12'R)-6-CHLORO-7'-HYDROXY-7'-(HYDROXYMETHYL)-11',12'-DIMETHYL-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.$0^{3,6}$.$0^{19,24}$]PENTACOSA[8,16,18,24]TETRAEN]-15'-ONE 13',13'-DIOXIDE

The AD-Mix-alpha mixture (640 mg, 0.43 mmol) was dissolved in a mixture of tert-butanol (10.0 mL) and water (10.0 mL) and cooled to 0 °C. (1S,3'R,6'R,8'E,11'S,12'R)-6-Chloro-11',12'-dimethyl-7'-methylidene-3,4-dihydro-2h,15'h-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (255 mg, 0.428 mmol) was added and the reaction mixture was warmed slowly to room temperature overnight. Another 5.0 mL of t-BuOH was added to homogenize the mixture. The reaction was stirred overnight. Another 320 mg of AD-Mix-alpha mixture was added and the reaction was stirred for an additional three days. The reaction was quenched by adding 575 mg of sodium sulfite at 0 °C and stirring for 45 minutes. The mixture was then extracted with EtOAc (2 x 25 mL). The combined organic layers were

washed with brine (1 x 20 mL) and dried over sodium sulfate. The crude product was then purified by chromatography (silica, 0 to 100% EtOAc (+0.3% HOAc):heptanes) to give (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(hydroxymethyl)-11',12'-dimethyl-3,4-dihydro-2h,15'h-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (31 mg, 12% yield). MS (ESI, +ve ion) *m/z* 629.2 $(M+H)^+$.

Step 3: (1S,3'R,6'R,11'S,12'R)-7'-((2-BROMOETHOXY)METHYL)-6-CHLORO-7'-HYDROXY-11',12'-DIMETHYL-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[16,18,24]TRIEN]-15'-ONE 13',13'-DIOXIDE

(1S,3'R,6'R,8'E,11'S,12'R)-6-Chloro-7'-hydroxy-7'-(hydroxymethyl)-11',12'-dimethyl-3,4-dihydro-2h,15'h-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (30.0 mg, 0.048 mmol) was dissolved in THF (1.0 mL) and cooled to 0 °C. Sodium hydride (60% dispersion, 19.0 mg, 0.48 mmol) was added and the resulting slurry was stirred for ten minutes, then 2-bromoethyl trifluoromethanesulfonate (Ark Pharm Inc.) (61 mg, 0.24 mmol) was added and the reaction was allowed to slowly warm to room temperature over 45 minutes. The reaction was then quenched with slow addition of water (5 mL) and the mixture was extracted (2 x 25 mL) with ethyl acetate. The combined organic layers were washed with brine (1 x 15 mL) and then dried over magnesium sulfate. The residue was then purified by chromatography (silica, 0 to 50% EtOAc (+0.3% HOAc) : hexanes) to give (1S,3'R,6'R,11'S,12'R)-7'-((2-bromoethoxy)methyl)-6-chloro-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2h,15'h-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide (25 mg, 71% yield). MS (ESI, +ve ion) *m/z* 739.1 $(M+H)^+$.

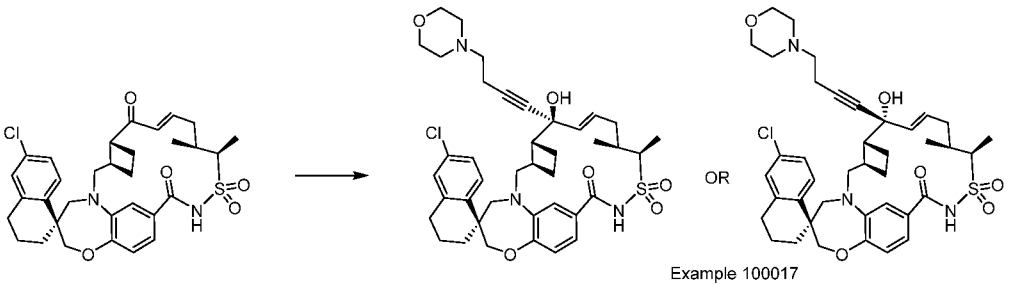
Step 4: (2S,3'R,6'R,11'S,12'R,22'S)-6"-CHLORO-11',12'-DIMETHYL-3",4"-DIHYDRO-2"H,15'H-DISPIRO[1,4-DIOXANE-2,7'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[16,18,24]TRIENE-22',1"-NAPHTHALEN]-15'-ONE 13',13'-DIOXIDE OR (2R,3'R,6'R,11'S,12'R,22'S)-6"-CHLORO-11',12'-DIMETHYL-3",4"-DIHYDRO-2"H,15'H-DISPIRO[1,4-DIOXANE-2,7'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.0~3,6~.0~19,24~]PENTACOSA[16,18,24]TRIENE-22',1"-NAPHTHALEN]-15'-ONE 13',13'-DIOXIDE

(1S,3'R,6'R,11'S,12'R)-7'-((2-Bromoethoxy)methyl)-6-chloro-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2h,15'h-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide (25.0 mg, 0.034 mmol) was then dissolved in DMF (0.5 mL) and sodium hydride (60% dispersion, 19 mg, 0.48 mmol) was added. This mixture was then heated to 85 °C for 10 minutes. The reaction mixture was then cooled to room temperature and quenched with dropwise addition of water (5 mL). This mixture was extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with 1 N LiCl solution (1 x 15 mL) and brine (1 x 10 mL) and dried over magnesium sulfate. The crude product was the purified by chromatography (silica, 0 to 50% EtOAc (+0.3% HOAc) : hexanes) to give (2S,3'R,6'R,11'S,12'R,22'S)-6"-chloro-11',12'-dimethyl-3",4"-dihydro-2"h,15'h-dispiro[1,4-dioxane-2,7'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-22',1"-naphthalen]-15'-one 13',13'-dioxide or (2R,3'R,6'R,11'S,12'R,22'S)-6"-chloro-11',12'-dimethyl-3",4"-dihydro-2"h,15'h-dispiro[1,4-dioxane-2,7'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-22',1"-naphthalen]-15'-one 13',13'-dioxide (14 mg, 45% yield). ^{1}H NMR (400MHz, MeOH) δ 7.73 (d, *J*=8.4 Hz, 1H), 7.17 (dd, *J*=2.2, 8.4 Hz, 1H), 7.13 - 7.08 (m, 2H), 7.02 (d, *J*=1.6 Hz, 1H), 6.92 (d, *J*=8.0 Hz, 1H), 4.08 (s, 2H), 4.06 - 4.01 (m, 1H), 3.76 (d, *J*=11.9 Hz, 2H), 3.73 - 3.59 (m, 4H), 3.58 - 3.49 (m, 1H), 3.46 - 3.38 (m, 1H), 3.23 - 3.15 (m, 1H), 3.10 (dd, *J*=9.1, 15.4 Hz, 1H), 2.86 -

2.68 (m, 2H), 2.62 - 2.50 (m, 1H), 2.11 - 2.03 (m, 1H), 1.96 - 1.84 (m, 3H), 1.76 - 1.51 (m, 7H), 1.49 - 1.40 (m, 1H), 1.36 (d, *J*=7.0 Hz, 3H), 1.34 - 1.27 (m, 2H), 1.23 - 1.19 (m, 2H), 1.01 (d, *J*=6.8 Hz, 3H). MS (ESI, +ve ion) *m/z* 657.2 $(M+H)^+$.

Example 100017

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(4-(4-morpholinyl)-1-butyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(4-(4-morpholinyl)-1-butyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide



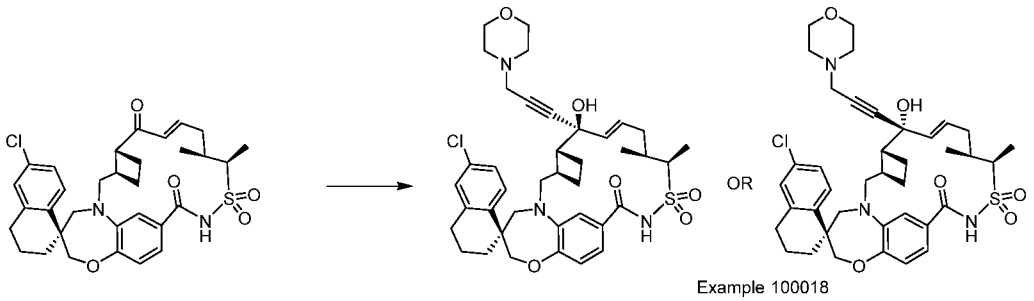
Example 100017

To a cooled (-78 °C) solution of 4-(but-3-yn-1-yl)morpholine (0.163 g, 1.171 mmol) in tetrahydrofuran (3 mL) was added 2.5 M butyllithium solution in toluene (0.400 mL, 1.00 mmol) dropwise via syringe. After 45 min, a solution of (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,7'H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7',15'-dione 13',13'-dioxide (0.100 g, 0.167 mmol) in THF (1 mL) was added dropwise. After 1 h, the reaction was quenched with saturated NH_4Cl (3 mL) and the mixture was warmed to room temperature. The mixture was extracted with dichloromethane (3x) and the combined organic layers were washed with

brine and dried over Na_2SO_4. The solution was filtered and the filtrate was concentrated under reduced pressure to give an orange oil. The crude material was purified by preparative SFC (Waters Thar 200; Cyano Column (21.1x250 mm, 5 µm) with 18% methanol (20 mM NH_3), 82% carbon dioxide; flow rate = 95 mL/min, column temperature = 40°C, pressure = 100 bar, detection at 220 nm) to give the first eluting diastereomer, (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(4-(4-morpholinyl)-1-butyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(4-(4-morpholinyl)-1-butyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (32 mg, 26%) as a white solid. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.72 (d, *J*=8.41 Hz, 1 H), 7.13 - 7.24 (m, 2 H), 7.09 (d, *J*=1.96 Hz, 1 H), 6.83 - 6.96 (m, 2 H), 6.25 - 6.41 (m, 1 H), 5.75 (d, *J*=15.26 Hz, 1 H), 4.38 (d, *J*=15.06 Hz, 1 H), 4.29 (q, *J*=7.37 Hz, 1 H), 3.97 - 4.13 (m, 2 H), 3.69 (d, *J*=14.08 Hz, 1 H), 3.58 (t, *J*=4.69 Hz, 4 H), 3.26 (d, *J*=14.28 Hz, 1 H), 3.00 (dd, *J*=15.26, 10.37 Hz, 1 H), 2.47 - 2.87 (m, 7 H), 2.29 - 2.46 (m, 5 H), 1.80 - 2.21 (m, 9 H), 1.61 - 1.72 (m, 1 H), 1.44 (d, *J*=7.24 Hz, 3 H), 1.33 - 1.41 (m, 1 H), 1.03 (d, *J*=6.85 Hz, 3 H). MS (ESI, +ve ion) *m/z* 736.2 $(M+1)^+$.

Example 100018

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(3-(4-morpholinyl)-1-propyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(3-(4-morpholinyl)-1-propyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide



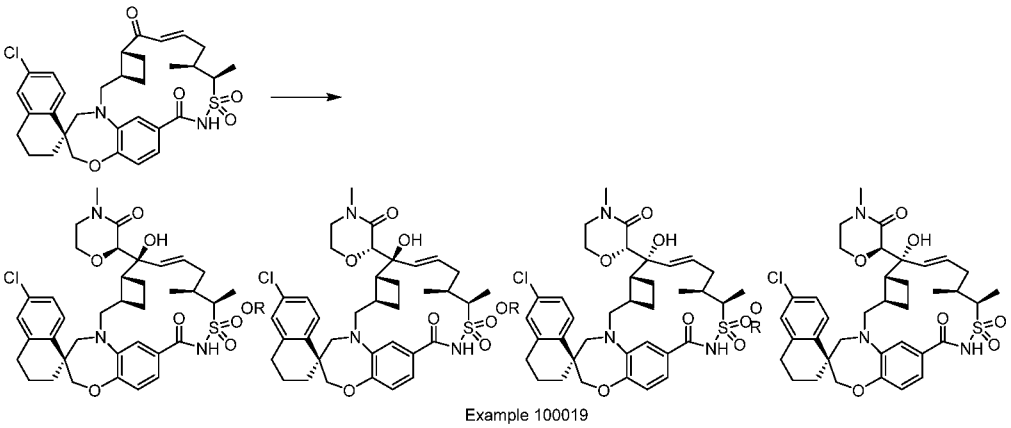
Example 100018

To a cooled (-78 °C) solution of 4-(prop-2-yn-1-yl)morpholine (0.170 mL, 1.35 mmol, Ark Pharm, Inc.) in tetrahydrofuran (3 mL) was added butyllithium solution (2.5 M in toluene, 0.500 mL, 1.25 mmol) dropwise via syringe. After 45 min a solution of (1S,3'R,6'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,7'H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7',15'-dione 13',13'-dioxide (0.100 g, 0.167 mmol) in THF (1 mL) was added dropwise. After 1 h, the reaction was quenched with saturated NH_4Cl (3 mL) and the mixture was warmed to room temperature. The mixture was extracted with DCM (3x) and the combined organic layers were washed with brine and dried over Na_2SO_4. The solution was filtered and the filtrate was concentrated under reduced pressure to give a yellow oil. The crude material was purified using preparative SFC (Premier (2 x 25 cm); 50% methanol/CO_2, 100 bar; 50 mL/min, 254 nm) to give the first eluting isomer, (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(3-(4-morpholinyl)-1-propyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(3-(4-morpholinyl)-1-propyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (40 mg, 33% yield) as a solid. ^1H NMR (400 MHz, CD_2Cl_2) δ 7.71 (d, *J*=8.41 Hz, 1 H), 7.12 - 7.23 (m, 2 H), 7.09 (d, *J*=2.15 Hz, 1 H), 6.84 - 6.97 (m, 2 H), 6.22 - 6.40 (m, 1 H), 5.78 (d, *J*=14.87 Hz, 1 H),

4.25 (d, *J*=14.67 Hz, 2 H), 4.07 (s, 2 H), 3.70 (d, *J*=14.28 Hz, 1 H), 3.59 - 3.66 (m, 4 H), 3.56 (s, 2 H), 3.25 (d, *J*=14.08 Hz, 1 H), 3.02 (dd, *J*=15.16, 10.47 Hz, 1 H), 2.67 - 2.89 (m, 2 H), 2.51 - 2.65 (m, 5 H), 2.33 - 2.49 (m, 1 H), 2.02 - 2.16 (m, 4 H), 1.76 - 2.01 (m, 7 H), 1.62 - 1.73 (m, 1 H), 1.43 (d, *J*=7.04 Hz, 3 H), 1.34 - 1.41 (m, 1 H), 1.04 (d, *J*=6.46 Hz, 3 H). MS (ESI, +ve ion) *m/z* 722.2 $(M+1)^+$.

Example 100019

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((2R)-4-methyl-3-oxo-2-morpholinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((2S)-4-methyl-3-oxo-2-morpholinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((2S)-4-methyl-3-oxo-2-morpholinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((2R)-4-methyl-3-oxo-2-morpholinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide



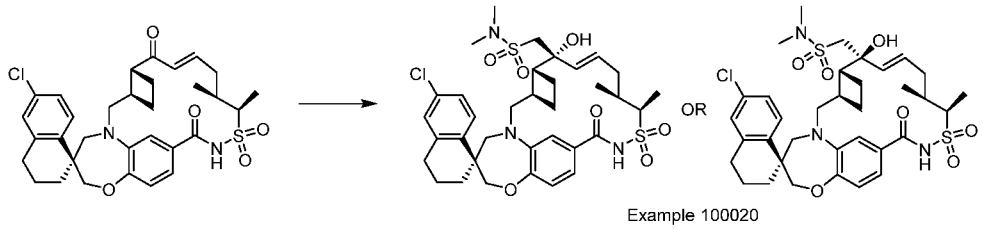
Example 100019

To a solution of diisopropylamine (1.183 mL, 8.44 mmol) in tetrahydrofuran (4.22 mL) at 0 °C was added butyllithium (2.5 M in hexanes, 3.38 mL, 8.44 mmol) for 3 minutes. The solution was then cooled to -78 °C. 4-Methyl-morpholin-3-one (0.887 mL, 8.44 mmol) was added dropwise and the solution was allowed to stir for 1 hour. (1S,3'R,6'R,8'E,11'S,12'R)-6-Chloro-11',12'-dimethyl-3,4-dihydro-2H,7'H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7',15'-dione 13',13'-dioxide (0.252 g, 0.422 mmol) in a solution of 0.5 mL of THF was added dropwise. Upon completion, saturated ammonium chloride aqueous solution was added. 1 N HCl was added until the pH reached 2-3 and the solution was extracted with EtOAc. The organic extract was washed with saturated NaCl, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was adsorbed onto a plug of silica gel and chromatographed through a Biotage SNAP Ultra silica gel column (50 g), eluting with a gradient of 10% to 100% EtOAc:EtOH (3:1) in hexane with 0.5% AcOH. The material was further purified by preparative SFC using a Me-sulfone achiral column (21x150 mm, 5 μm), 60% methanol with 20 mM NH_3, flow rate 60 mL/min, column temperature 40 °C, pressure 100 bar, detection at 220 nm. The third isomer to elute was isolated to give (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((2R)-4-methyl-3-oxo-2-morpholinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,2

4]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((2S)-4-methyl-3-oxo-2-morpholinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((2S)-4-methyl-3-oxo-2-morpholinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((2R)-4-methyl-3-oxo-2-morpholinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.92 (d, J=6.06 Hz, 3 H) 1.02 (br. s., 2 H) 1.36 (t, J=12.72 Hz, 1 H) 1.61 (br. s., 3 H) 1.87 (br. s., 3 H) 1.92 - 2.13 (m, 3 H) 2.25 (d, J=7.63 Hz, 1 H) 2.62 - 2.79 (m, 2 H) 2.84 (s, 3 H) 2.86 - 3.06 (m, 3 H) 3.29 (br. s., 1 H) 3.55 (d, J=13.50 Hz, 1 H) 3.71 (br. s., 1 H) 3.79 - 4.01 (m, 4 H) 4.10 (d, J=13.30 Hz, 1 H) 4.26 (br. s., 1 H) 5.33 (br. s., 1 H) 5.71 (d, J=15.45 Hz, 1 H) 6.17 (br. s., 1 H) 6.67 - 6.84 (m, 1 H) 6.98 - 7.41 (m, 4 H) 7.65 (d, J=8.61 Hz, 1 H). MS (ESI, +ve ion) m/z 712.2 $(M+1)^+$.

Example 100020

1-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-dimethylmethanesulfonamide OR 1-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-dimethylmethanesulfonamide



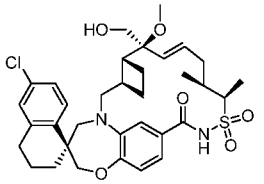
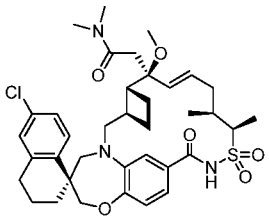
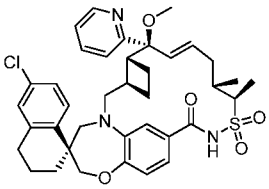
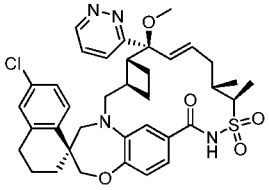
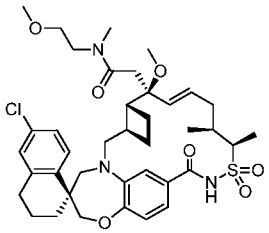
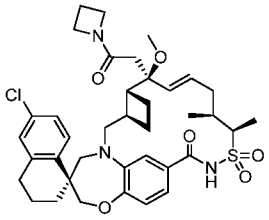
Example 100020

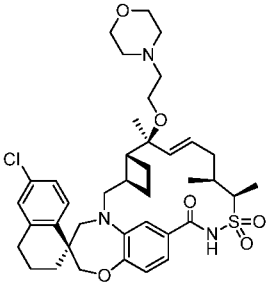
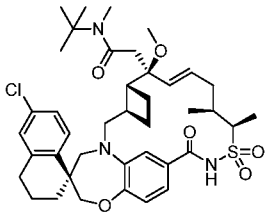
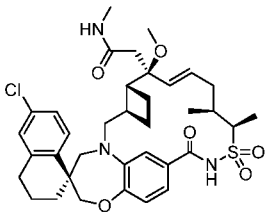
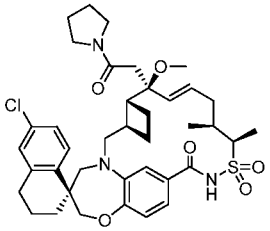
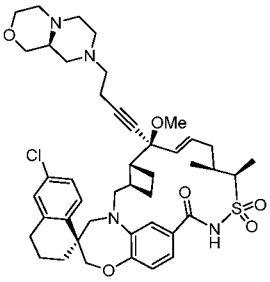
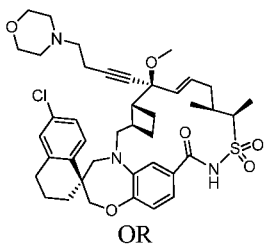
To a solution of N,N-dimethylmethanesulfonamide (206 mg, 1.68 mmol) in 2-methyltetrahydrofuran (4 mL) at 0 °C was added n-butyllithium (1.6 M in hexanes, 0.67 mL, 1.7 mmol), and the reaction was stirred at 0 °C for 5 min. (1S,3'R,6'R,8'E,11'S,12'R)-6-Chloro-11',12'-dimethyl-3,4-dihydro-2H,7'H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7',15'-dione 13',13'-dioxide (100 mg, 0.167 mmol) in 2-methyltetrahydrofuran (1 mL) was added at low temperature and after 15 min quenched with aqueous saturated NH_4Cl (50 mL), brine (50 mL) and EtOAc (100 mL). The organic layer was separated, dried (Na_2SO_4), filtered and concentrated onto silica. Purification by silica gel chromatography (0 to 100% EtOAc (0.3% AcOH) in heptane afforded 1-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-dimethylmethanesulfonamide and 1-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-dimethylmethanesulfonamide (70 mg, 0.10 mmol, 58% yield) as a mixture of isomers. The mixture was then purified by preparatory SFC chromatography (column: Welko-O1 250 mm x 21 mm column, mobile phase: 65:35 (A:B) isocratic, A: liquid CO_2, B: methanol (20 mM NH_3), flow rate: 70 g/min, column temperature: 40 °C, detection: UV at 220 nm), and the first eluting isomer 1-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-

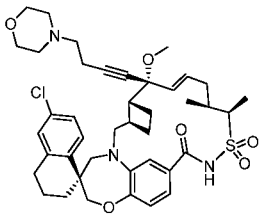
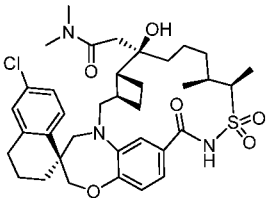
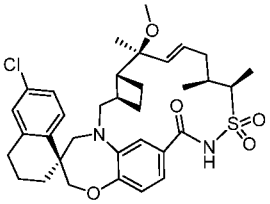
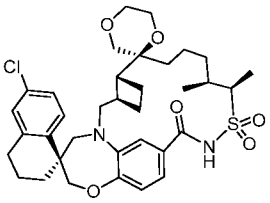
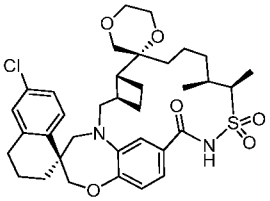
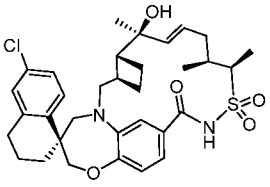
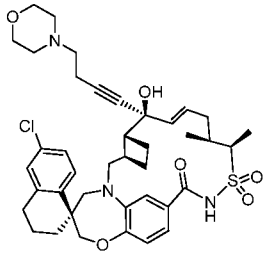
[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-dimethylmethanesulfonamide OR 1-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-dimethylmethanesulfonamide (10 mg, 0.014 mmol, 8% yield) was isolated. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.69 (d, *J*=8.41 Hz, 1H), 7.17 (dd, *J*=2.25, 8.51 Hz, 1H), 7.09 (d, *J*=2.15 Hz, 1H), 6.94 (s, 2H), 6.87 (s, 1H), 5.68-5.80 (m, 2H), 4.00-4.22 (m, 4H), 3.67-3.83 (m, 2H), 3.57 (br d, *J*=14.48 Hz, 1H), 3.20-3.32 (m, 2H), 3.05-3.16 (m, 1H), 2.96 (s, 6H), 2.89-2.93 (m, 1H), 2.69-2.83 (m, 2H), 2.38-2.50 (m, 1H), 2.03-2.17 (m, 3H), 1.85-2.02 (m, 3H), 1.72-1.84 (m, 2H), 1.58-1.70 (m, 2H), 1.46 (d, *J*=7.24 Hz, 3H), 1.32-1.41 (m, 1H), 1.06 (d, *J*=6.06 Hz, 3H). One exchangeable proton was not observed. MS (ESI, +ve ion) *m/z* 720.2 $(M+H)^+$.

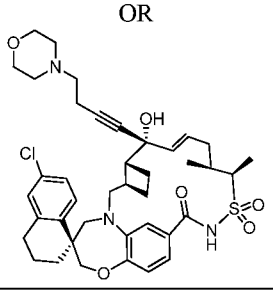
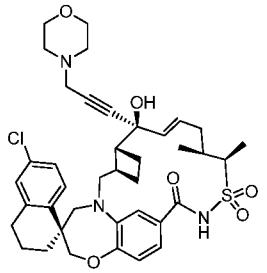
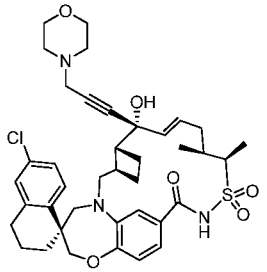
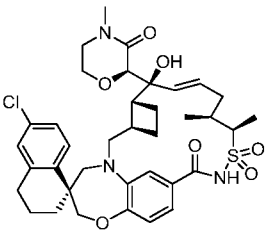
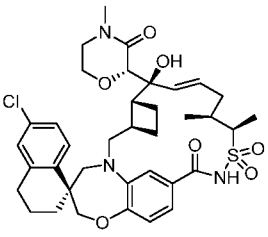
Table 2 lists compounds prepared by the General Methods outlined in the present specification.

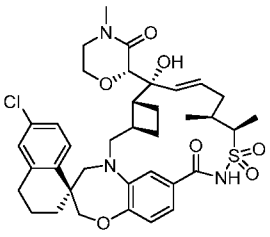
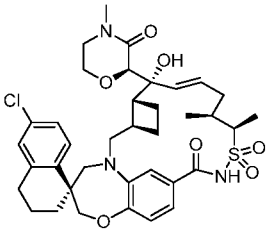
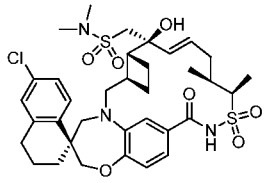
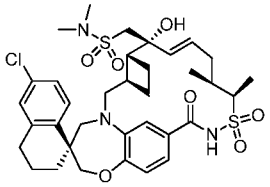
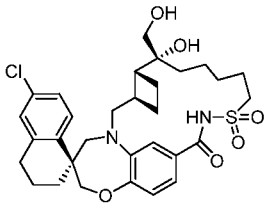
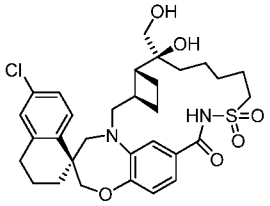
TABLE 2: Examples Prepared by the General Methods

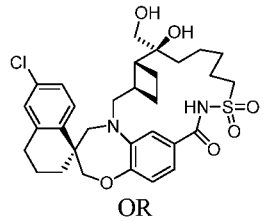
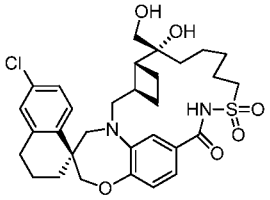
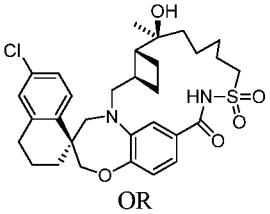
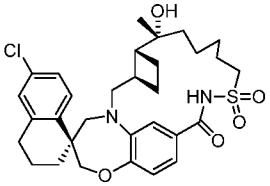
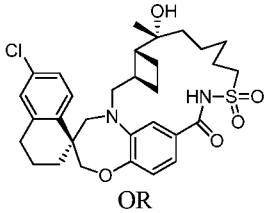
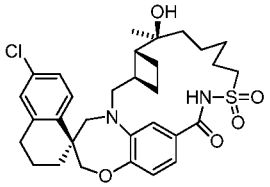
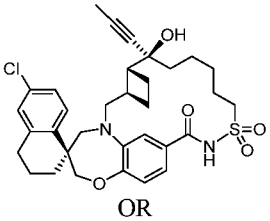
Example Number	Structure	Name	MS Data $(M+1)^+$ Unless Noted Otherwise
100001		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(hydroxymethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	643.2
100002		2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-dimethylacetamide	698.2
100003		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	690.2
100004		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(3-pyridazinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	691.2
100005		2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N-(2-methoxyethyl)-N-methylacetamide	742.2
100006		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-7'-(2-(1-azetidinyl)-2-oxoethyl)-6-chloro-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	710.2

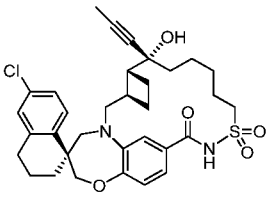
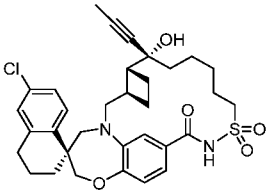
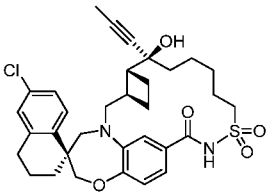
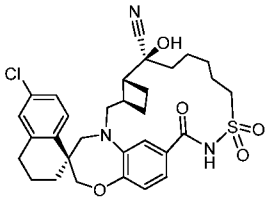
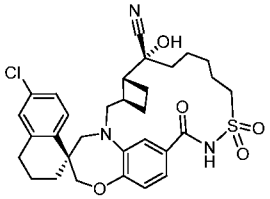
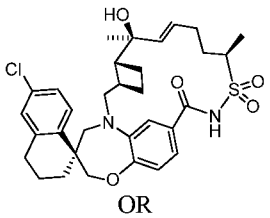
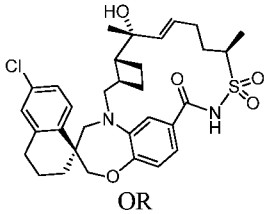
100007		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7',11',12'-trimethyl-7'-(2-(4-morpholinyl)ethoxy)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	726.3
100008		2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N-methyl-N-(2-methyl-2-propanyl)acetamide	762.3
100009		2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N-methylacetamide	684.2
100010		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-oxo-2-(1-pyrrolidinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	724.2
100011		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(4-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-1-butyn-1-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	805.3
100012	 OR	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(4-(4-morpholinyl)-1-butyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(4-(4-	750.3

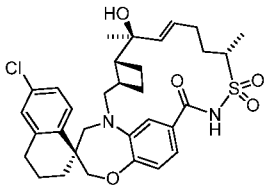
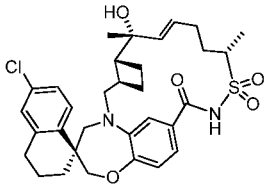
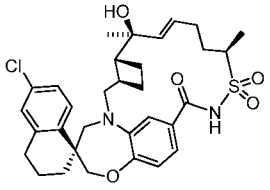
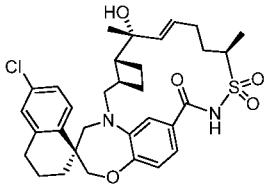
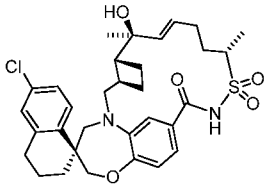
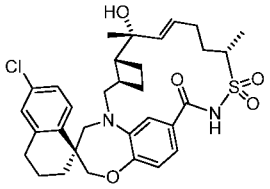
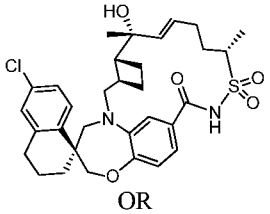
		morpholinyl)-1-butyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100013		2-((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N,N-dimethylacetamide	686.2
100014		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	627.2
100015	 OR 	(2S,3'R,6'R,11'S,12'R,22'S)-6"-chloro-11',12'-dimethyl-3",4"-dihydro-2"H,15'H-dispiro[1,4-dioxane-2,7'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-22',1"-naphthalen]-15'-one 13',13'-dioxide OR (2R,3'R,6'R,11'S,12'R,22'S)-6"-chloro-11',12'-dimethyl-3",4"-dihydro-2"H,15'H-dispiro[1,4-dioxane-2,7'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-22',1"-naphthalen]-15'-one 13',13'-dioxide	657.2
100016		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	613.1
100017		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(4-(4-morpholinyl)-1-butyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR	736.2

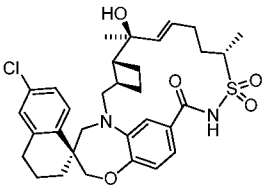
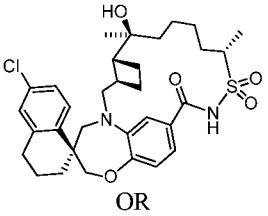
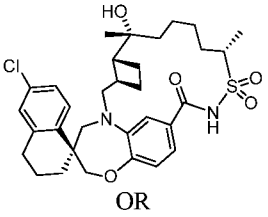
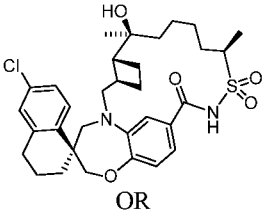
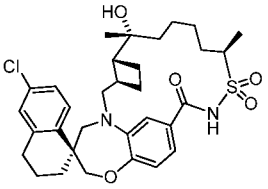
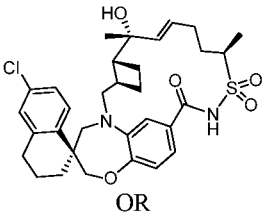
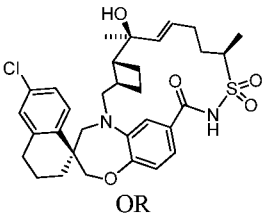
	OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(4-(4-morpholinyl)-1-butyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100018	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(3-(4-morpholinyl)-1-propyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(3-(4-morpholinyl)-1-propyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	722.2
100019	 OR  OR	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((2R)-4-methyl-3-oxo-2-morpholinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((2S)-4-methyl-3-oxo-2-morpholinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((2S)-4-methyl-3-oxo-2-morpholinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7	712.2

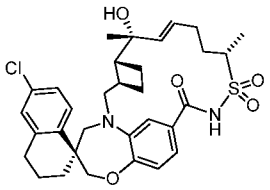
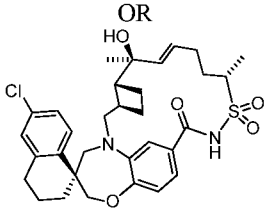
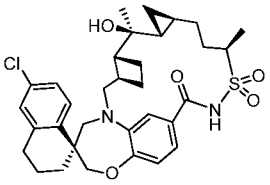
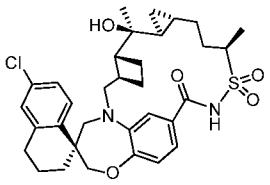
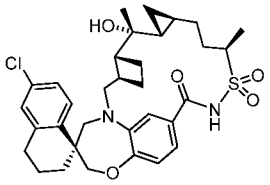
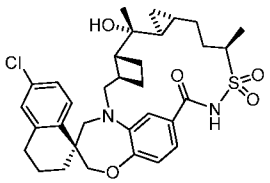
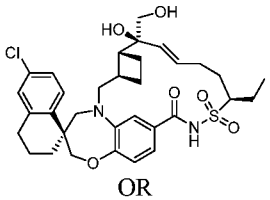
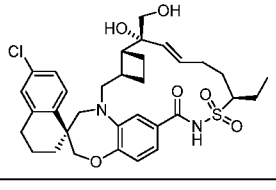
	 OR 	.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((2R)-4-methyl-3-oxo-2-morpholinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100020	 OR 	1-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-dimethylmethanesulfonamide OR 1-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-dimethylmethanesulfonamide	720.2
100021	 OR 	(1S,3'R,6'R,7'R)-6-chloro-7'-hydroxy-7'-(hydroxymethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S)-6-chloro-7'-hydroxy-7'-(hydroxymethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	602.9

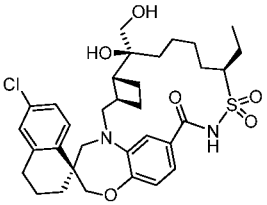
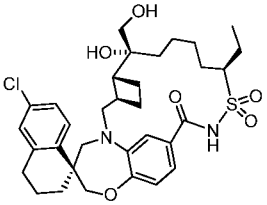
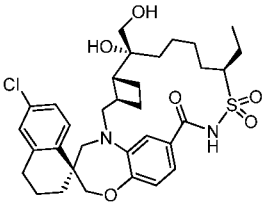
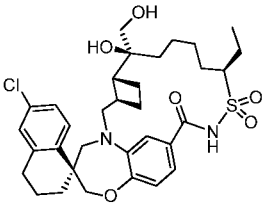
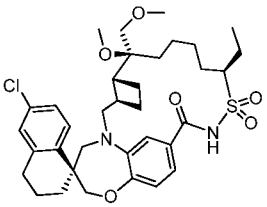
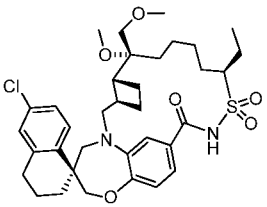
100022	 OR 	(1S,3'R,6'R,7'S)-6-chloro-7'-hydroxy-7'-(hydroxymethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R)-6-chloro-7'-hydroxy-7'-(hydroxymethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	603.0
100023	 OR 	(1S,3'R,6'R,7'S)-6-chloro-7'-hydroxy-7'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R)-6-chloro-7'-hydroxy-7'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	587.2
100024	 OR 	(1S,3'R,6'R,7'R)-6-chloro-7'-hydroxy-7'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S)-6-chloro-7'-hydroxy-7'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	587.3
100025	 OR	(1S,3'R,6'R,7'S)-6-chloro-7'-hydroxy-7'-(1-propyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R)-6-chloro-7'-hydroxy-7'-(1-propyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7	611.0

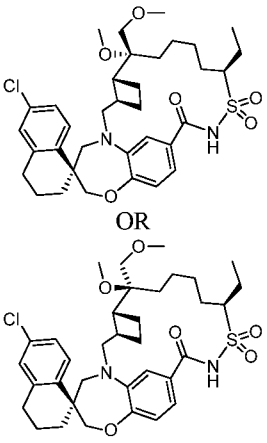
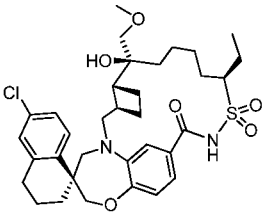
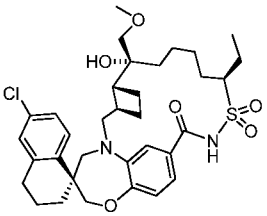
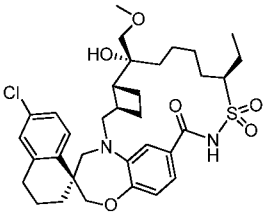
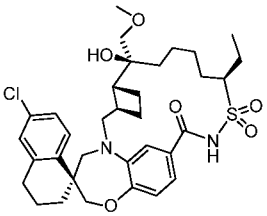
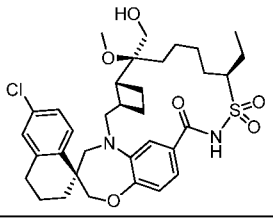
		.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	
100026	 OR 	(1S,3'R,6'R,7'R)-6-chloro-7'-hydroxy-7'-(1-propyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S)-6-chloro-7'-hydroxy-7'-(1-propyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	611.0
100027	 OR 	(1S,3'R,6'R,7'S)-6-chloro-7'-hydroxy-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene]-7'-carbonitrile 13',13'-dioxide OR (1S,3'R,6'R,7'R)-6-chloro-7'-hydroxy-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene]-7'-carbonitrile 13',13'-dioxide	598.0
100028	 OR  OR	(1S,3'R,6'R,7'S,8'E,12'S)-6-chloro-7'-hydroxy-7',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,12'R)-6-chloro-7'-hydroxy-7',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,12'S)-6-chloro-7'-hydroxy-7',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7	599.2

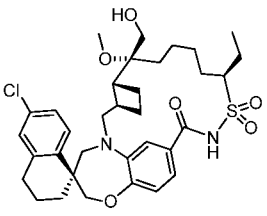
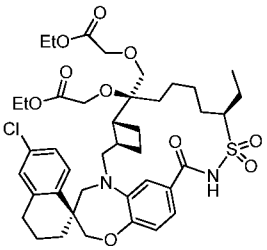
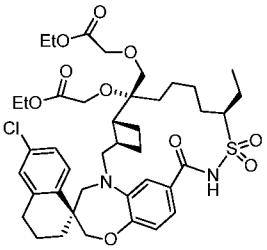
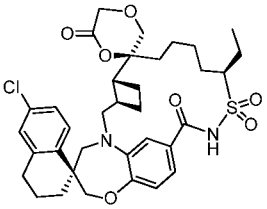
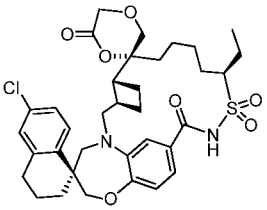
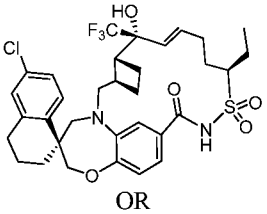
	 OR 	.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,12'R)-6-chloro-7'-hydroxy-7',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100029	 OR  OR  OR 	(1S,3'R,6'R,7'S,8'E,12'S)-6-chloro-7'-hydroxy-7',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,12'R)-6-chloro-7'-hydroxy-7',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,12'S)-6-chloro-7'-hydroxy-7',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,12'R)-6-chloro-7'-hydroxy-7',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	599.2
100030	 OR	(1S,3'R,6'R,7'R,8'E,12'S)-6-chloro-7'-hydroxy-7',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,12'S)-6-chloro-7'-hydroxy-7',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7	599.2

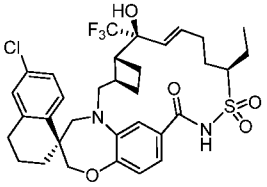
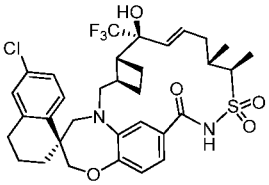
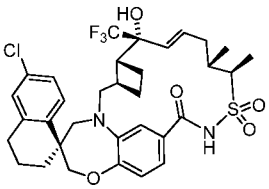
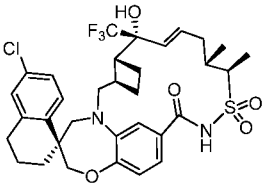
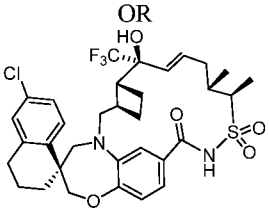
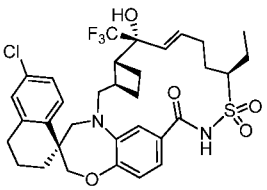
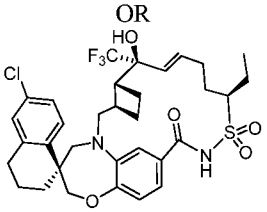
		.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100031	 OR  OR  OR 	(1S,3'R,6'R,7'S,12'S)-6-chloro-7'-hydroxy-7',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,12'R)-6-chloro-7'-hydroxy-7',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,12'S)-6-chloro-7'-hydroxy-7',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,12'R)-6-chloro-7'-hydroxy-7',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	601.2
100032	 OR  OR	(1S,3'R,6'R,7'R,8'E,12'S)-6-chloro-7'-hydroxy-7',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,12'R)-6-chloro-7'-hydroxy-7',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,12'S)-6-chloro-7'-hydroxy-7',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7	599.2

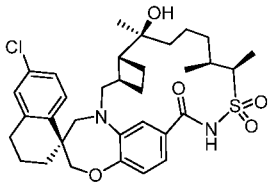
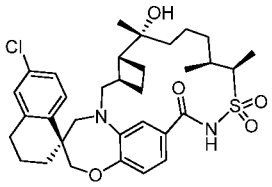
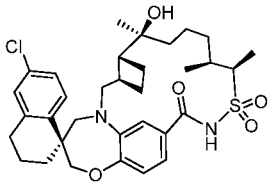
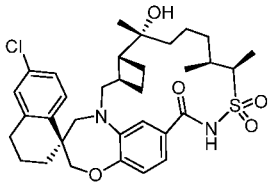
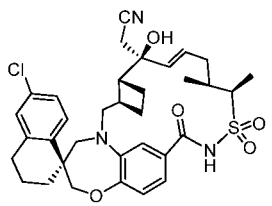
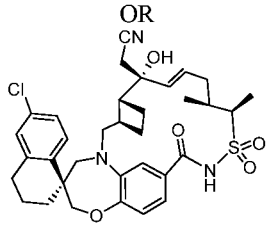
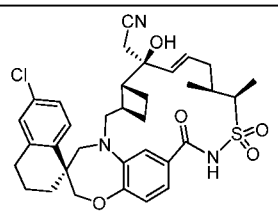
	 OR 	.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,12'R)-6-chloro-7'-hydroxy-7',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100033	 OR  OR  OR 	(1S,3'R,6'R,7'S,8'S,13'R)-6-chloro-7'-hydroxy-7',13'-dimethyl-3,4-dihydro-2H,16'H-spiro[naphthalene-1,23'-[21]oxa[14]thia[1,15]diazapentacyclo[15.7.2.0~3,6~.0~8,10~.0~20,25~]hexacosa[17,19,25]trien]-16'-one 14',14'-dioxide OR (1S,3'R,6'R,7'S,8'S,13'R)-6-chloro-7'-hydroxy-7',13'-dimethyl-3,4-dihydro-2H,16'H-spiro[naphthalene-1,23'-[21]oxa[14]thia[1,15]diazapentacyclo[15.7.2.0~3,6~.0~8,10~.0~20,25~]hexacosa[17,19,25]trien]-16'-one 14',14'-dioxide OR (1S,3'R,6'R,7'R,8'R,10'R,13'R)-6-chloro-7'-hydroxy-7',13'-dimethyl-3,4-dihydro-2H,16'H-spiro[naphthalene-1,23'-[21]oxa[14]thia[1,15]diazapentacyclo[15.7.2.0~3,6~.0~8,10~.0~20,25~]hexacosa[17,19,25]trien]-16'-one 14',14'-dioxide OR (1S,3'R,6'R,7'R,8'R,10'R,13'R)-6-chloro-7'-hydroxy-7',13'-dimethyl-3,4-dihydro-2H,16'H-spiro[naphthalene-1,23'-[21]oxa[14]thia[1,15]diazapentacyclo[15.7.2.0~3,6~.0~8,10~.0~20,25~]hexacosa[17,19,25]trien]-16'-one 14',14'-dioxide	613.2
100034	 OR 	(1S,3'R,6'R,7'S,8'E,12'R)-6-chloro-12'-ethyl-7'-hydroxy-7'-(hydroxymethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,12'R)-6-chloro-12'-ethyl-7'-hydroxy-7'-(hydroxymethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7	629.0

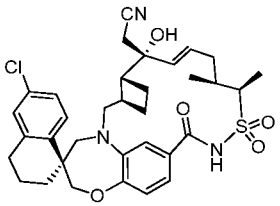
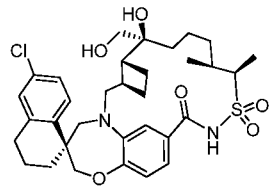
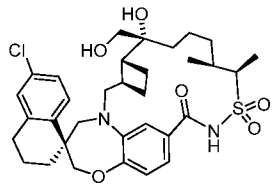
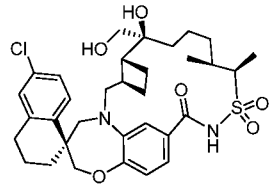
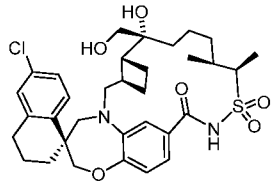
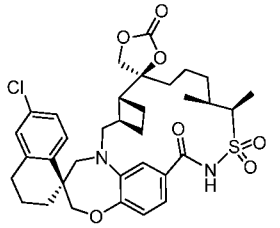
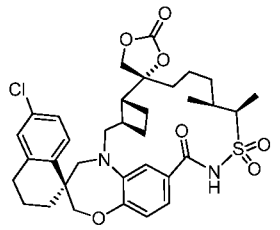
		.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100035	 OR 	(1S,3'R,6'R,7'S,12'R)-6-chloro-12'-ethyl-7'-hydroxy-7'-(hydroxymethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,12'R)-6-chloro-12'-ethyl-7'-hydroxy-7'-(hydroxymethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	631.1
100036	 OR 	(1S,3'R,6'R,7'R,12'R)-6-chloro-12'-ethyl-7'-hydroxy-7'-(hydroxymethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,12'R)-6-chloro-12'-ethyl-7'-hydroxy-7'-(hydroxymethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	631.1
100037	 OR 	(1S,3'R,6'R,7'S,12'R)-6-chloro-12'-ethyl-7'-methoxy-7'-(methoxymethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,12'R)-6-chloro-12'-ethyl-7'-methoxy-7'-(methoxymethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	659.1

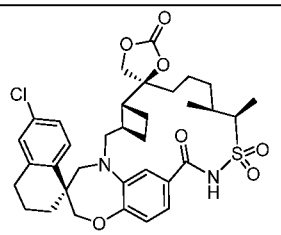
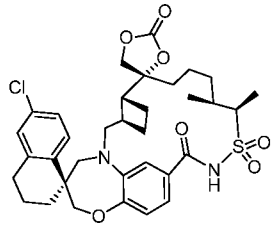
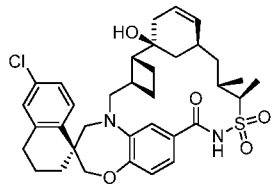
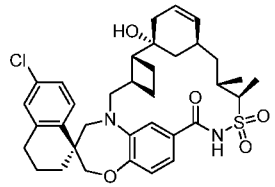
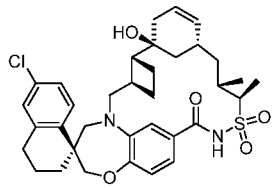
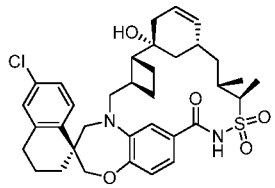
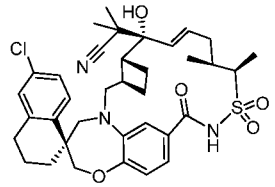
100038	 OR	(1S,3'R,6'R,7'R,12'R)-6-chloro-12'-ethyl-7'-methoxy-7'-(methoxymethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,12'R)-6-chloro-12'-ethyl-7'-methoxy-7'-(methoxymethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	659.1
100039	 OR 	(1S,3'R,6'R,7'S,12'R)-6-chloro-12'-ethyl-7'-hydroxy-7'-(methoxymethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,12'R)-6-chloro-12'-ethyl-7'-hydroxy-7'-(methoxymethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	645.1
100040	 OR 	(1S,3'R,6'R,7'R,12'R)-6-chloro-12'-ethyl-7'-hydroxy-7'-(methoxymethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,12'R)-6-chloro-12'-ethyl-7'-hydroxy-7'-(methoxymethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	645.1
100041		(1S,3'R,6'R,7'S,12'R)-6-chloro-12'-ethyl-7'-(hydroxymethyl)-7'-methoxy-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	645.1

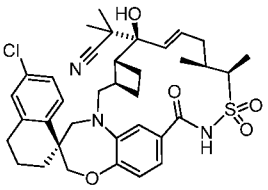
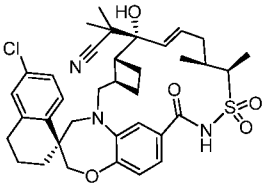
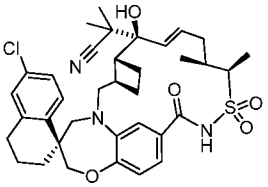
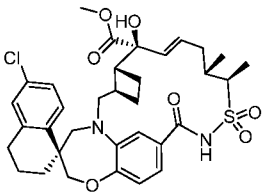
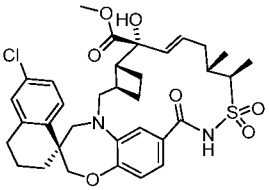
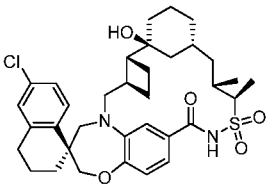
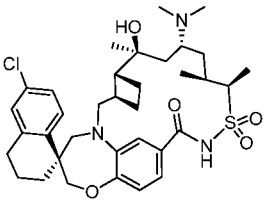
	OR 	OR (1S,3'R,6'R,7'R,12'R)-6-chloro-12'-ethyl-7'-(hydroxymethyl)-7'-methoxy-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	
100042	 OR 	ethyl (((1S,3'R,6'R,7'S,12'R)-6-chloro-7'-(2-ethoxy-2-oxoethoxy)-12'-ethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)methoxy)acetate OR ethyl (((1S,3'R,6'R,7'R,12'R)-6-chloro-7'-(2-ethoxy-2-oxoethoxy)-12'-ethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)methoxy)acetate	803.1
100043	 OR 	(2S,3'R,6'R,12'R,22'S)-6"-chloro-12'-ethyl-3",4"-dihydro-2"H,6H,15'H-dispiro[1,4-dioxane-2,7'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-22',1"-naphthalene]-6,15'-dione 13',13'-dioxide OR (2R,3'R,6'R,12'R,22'S)-6"-chloro-12'-ethyl-3",4"-dihydro-2"H,6H,15'H-dispiro[1,4-dioxane-2,7'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-22',1"-naphthalene]-6,15'-dione 13',13'-dioxide	671.0
100044	 OR	(1S,3'R,6'R,7'R,8'E,12'R)-6-chloro-12'-ethyl-7'-hydroxy-7'-(trifluoromethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,12'R)-6-chloro-12'-ethyl-7'-hydroxy-7'-(trifluoromethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-	667.0

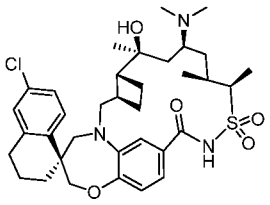
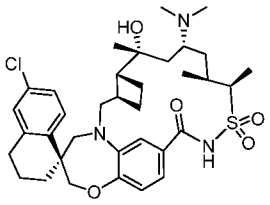
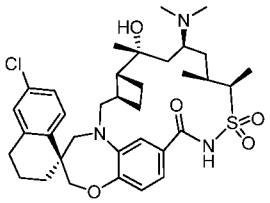
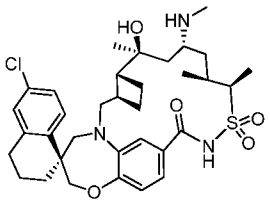
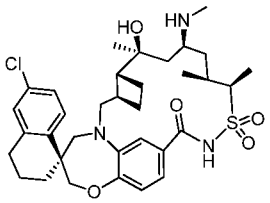
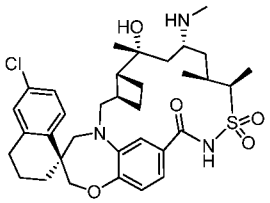
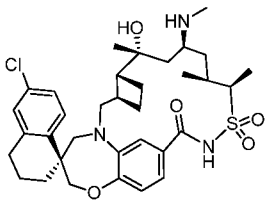
		[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100045	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(trifluoromethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(trifluoromethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	667.3
100046	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(trifluoromethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(trifluoromethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	667.3
100047	 OR 	(1S,3'R,6'R,7'R,8'E,12'R)-6-chloro-12'-ethyl-7'-hydroxy-7'-(trifluoromethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,12'R)-6-chloro-12'-ethyl-7'-hydroxy-7'-(trifluoromethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	667.0

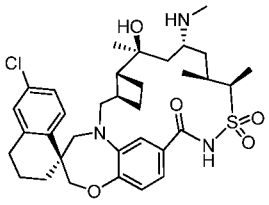
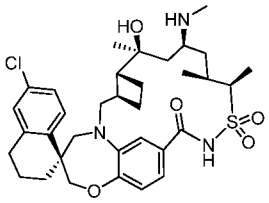
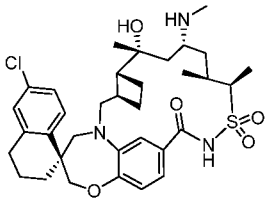
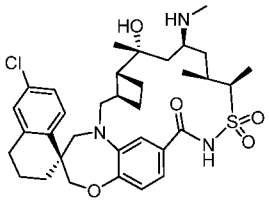
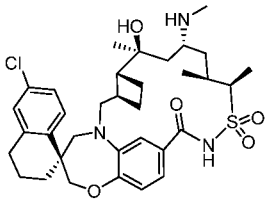
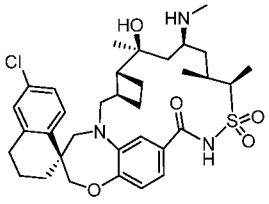
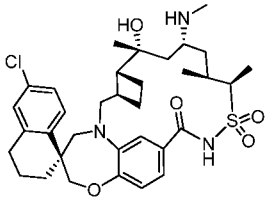
100048	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	615.2
100049	 OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	615.2
100050	 OR 	((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetonitrile OR ((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetonitrile	638.3
100051	 OR	((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetonitrile OR	638.2

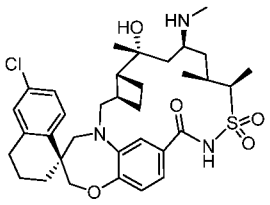
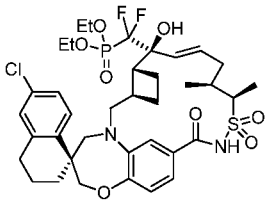
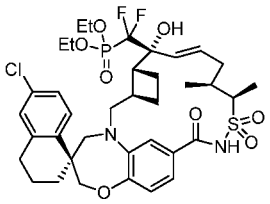
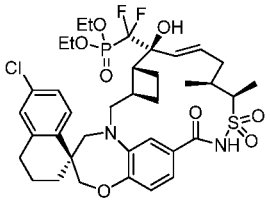
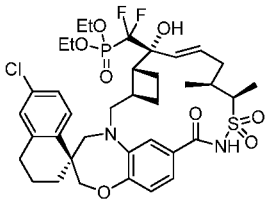
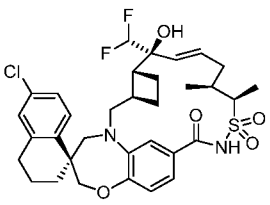
		((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetonitrile	
100052	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-7'-(hydroxymethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-7'-(hydroxymethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	631.2
100053	 OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-7'-(hydroxymethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-7'-(hydroxymethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	631.3
100054	 OR 	(3'R,4S,6'R,11'S,12'R,22'S)-6"-chloro-11',12'-dimethyl-3",4"-dihydro-2"H,15'H-dispiro[1,3-dioxolane-4,7'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-22',1"-naphthalene]-2,15'-dione 13',13'-dioxide OR (3'R,4R,6'R,11'S,12'R,22'S)-6"-chloro-11',12'-dimethyl-3",4"-dihydro-2"H,15'H-dispiro[1,3-dioxolane-4,7'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-22',1"-naphthalene]-2,15'-dione 13',13'-dioxide	657.3

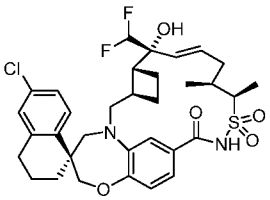
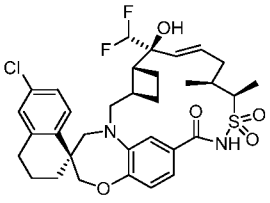
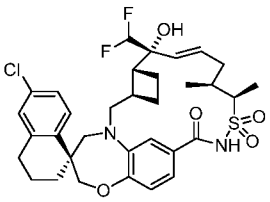
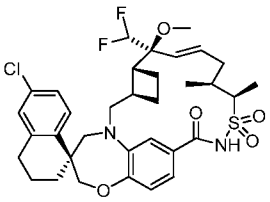
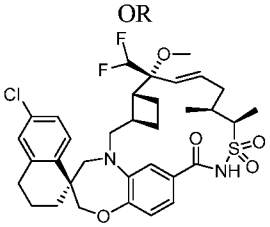
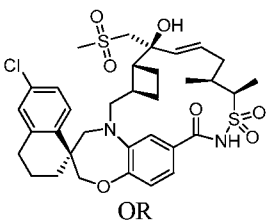
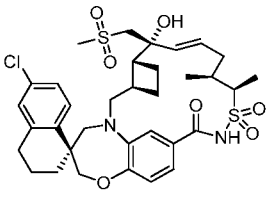
100055	 OR 	(3'R,4R,6'R,11'S,12'R,22'S)-6"-chloro-11',12'-dimethyl-3",4"-dihydro-2"H,15'H-dispiro[1,3-dioxolane-4,7'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-22',1"-naphthalene]-2,15'-dione 13',13'-dioxide OR (3'R,4S,6'R,11'S,12'R,22'S)-6"-chloro-11',12'-dimethyl-3",4"-dihydro-2"H,15'H-dispiro[1,3-dioxolane-4,7'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-22',1"-naphthalene]-2,15'-dione 13',13'-dioxide	657.3
100056	 OR 	(1S,3'R,6'R,7'S,11'S,13'S,14'R)-6-chloro-7'-hydroxy-13',14'-dimethyl-3,4-dihydro-2H,17'H-spiro[naphthalene-1,24'-[22]oxa[15]thia[1,16]diazapentacyclo[16.7.2.1~7,11~.0~3,6~.0~21,26~]octacosa[9,18,20,26]tetraen]-17'-one 15',15'-dioxide OR (1S,3'R,6'R,7'R,11'S,13'S,14'R)-6-chloro-7'-hydroxy-13',14'-dimethyl-3,4-dihydro-2H,17'H-spiro[naphthalene-1,24'-[22]oxa[15]thia[1,16]diazapentacyclo[16.7.2.1~7,11~.0~3,6~.0~21,26~]octacosa[9,18,20,26]tetraen]-17'-one 15',15'-dioxide	639.1
100057		(1S,3'R,6'R,7'S,11'R,13'S,14'R)-6-chloro-7'-hydroxy-13',14'-dimethyl-3,4-dihydro-2H,17'H-spiro[naphthalene-1,24'-[22]oxa[15]thia[1,16]diazapentacyclo[16.7.2.1~7,11~.0~3,6~.0~21,26~]octacosa[9,18,20,26]tetraen]-17'-one 15',15'-dioxide	639.1
100058		(1S,3'R,6'R,7'R,11'S,13'S,14'R)-6-chloro-7'-hydroxy-13',14'-dimethyl-3,4-dihydro-2H,17'H-spiro[naphthalene-1,24'-[22]oxa[15]thia[1,16]diazapentacyclo[16.7.2.1~7,11~.0~3,6~.0~21,26~]octacosa[9,18,20,26]tetraen]-17'-one 15',15'-dioxide	639.0
100059	 OR	2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-2-methylpropanenitrile OR 2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-	666.3

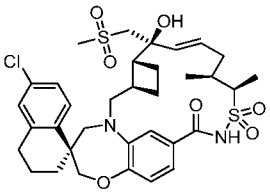
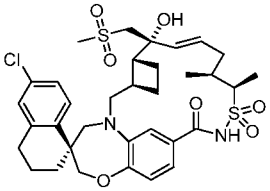
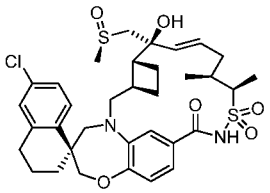
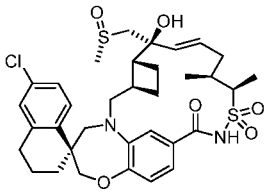
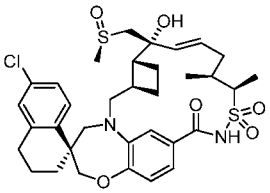
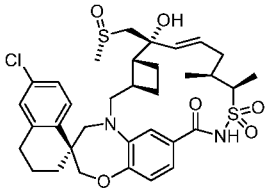
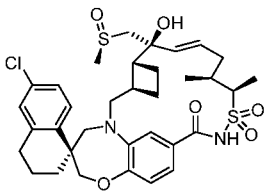
		13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-2-methylpropanenitrile	
100060	 OR 	2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-2-methylpropanenitrile OR 2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-2-methylpropanenitrile	666.3
100061	 OR 	methyl (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carboxylate 13',13'-dioxide OR methyl (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carboxylate 13',13'-dioxide	657.3
100062		(1S,3'R,6'R,7'S,11'R,13'S,14'R)-6-chloro-7'-hydroxy-13',14'-dimethyl-3,4-dihydro-2H,17'H-spiro[naphthalene-1,24'-[22]oxa[15]thia[1,16]diazapentacyclo[16.7.2.1~7,11~.0~3,6~.0~21,26~]octacosa[18,20,26]trien]-17'-one 15',15'-dioxide	641.1
100063	 OR	(1S,3'R,6'R,7'S,9'R,11'S,12'R)-6-chloro-9'-(dimethylamino)-7'-hydroxy-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,9'S,11'S,12'R)-6-chloro-9'-(dimethylamino)-7'-hydroxy-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-	657.8

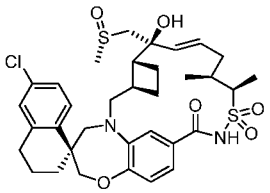
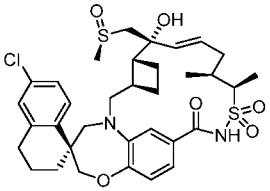
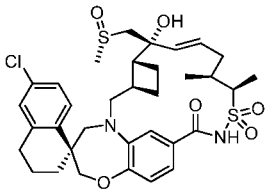
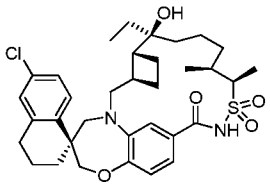
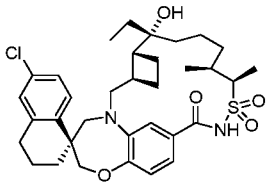
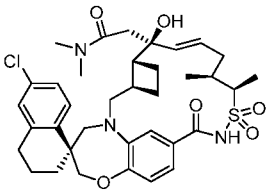
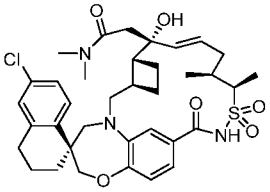
	 OR  OR 	spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,9'R,11'S,12'R)-6-chloro-9'-(dimethylamino)-7'-hydroxy-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,9'S,11'S,12'R)-6-chloro-9'-(dimethylamino)-7'-hydroxy-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	
100064	 OR  OR  OR 	(1S,3'R,6'R,7'S,9'R,11'S,12'R)-6-chloro-7'-hydroxy-7',11',12'-trimethyl-9'-(methylamino)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,9'S,11'S,12'R)-6-chloro-7'-hydroxy-7',11',12'-trimethyl-9'-(methylamino)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,9'R,11'S,12'R)-6-chloro-7'-hydroxy-7',11',12'-trimethyl-9'-(methylamino)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,9'S,11'S,12'R)-6-chloro-7'-hydroxy-7',11',12'-trimethyl-9'-(methylamino)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	644.2

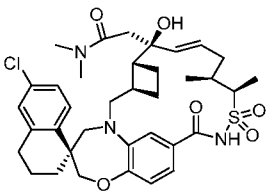
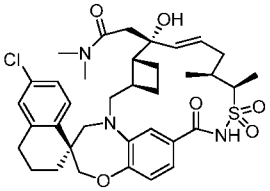
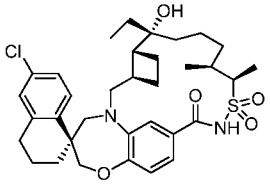
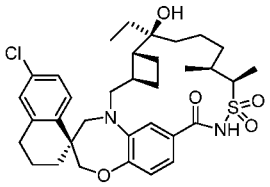
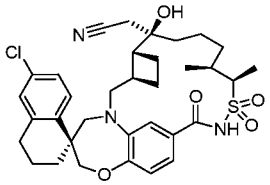
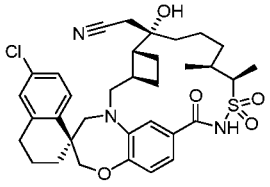
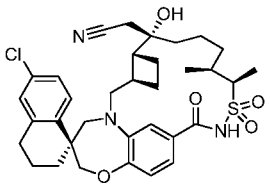
100065	 OR  OR  OR 	(1S,3'R,6'R,7'S,9'R,11'S,12'R)-6-chloro-7'-hydroxy-7',11',12'-trimethyl-9'-(methylamino)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,9'S,11'S,12'R)-6-chloro-7'-hydroxy-7',11',12'-trimethyl-9'-(methylamino)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,9'R,11'S,12'R)-6-chloro-7'-hydroxy-7',11',12'-trimethyl-9'-(methylamino)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,9'S,11'S,12'R)-6-chloro-7'-hydroxy-7',11',12'-trimethyl-9'-(methylamino)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	644.2
100066	 OR  OR  OR	(1S,3'R,6'R,7'S,9'R,11'S,12'R)-6-chloro-7'-hydroxy-7',11',12'-trimethyl-9'-(methylamino)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,9'S,11'S,12'R)-6-chloro-7'-hydroxy-7',11',12'-trimethyl-9'-(methylamino)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,9'R,11'S,12'R)-6-chloro-7'-hydroxy-7',11',12'-trimethyl-9'-(methylamino)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR	643.8

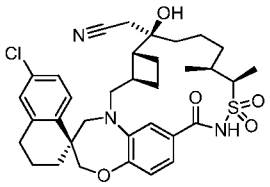
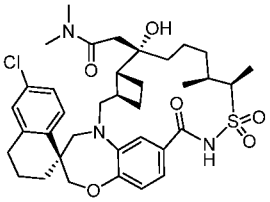
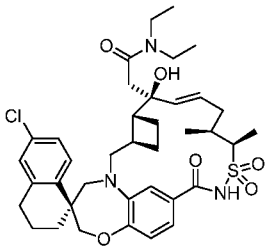
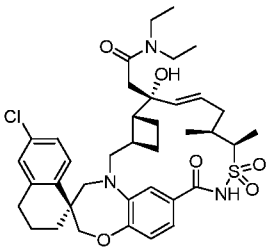
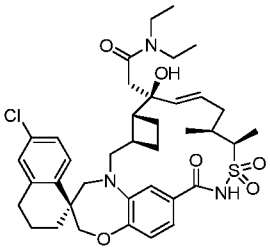
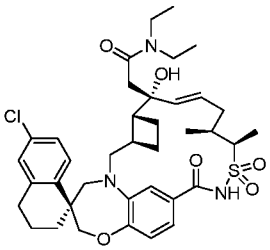
		(1S,3'R,6'R,7'R,9'S,11'S,12'R)-6-chloro-7'-hydroxy-7',11',12'-trimethyl-9'-(methylamino)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	
100067	 OR 	diethyl (((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)(difluoro)methyl)phosphonate OR diethyl (((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)(difluoro)methyl)phosphonate	785.2
100068	 OR 	diethyl (((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)(difluoro)methyl)phosphonate OR diethyl (((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)(difluoro)methyl)phosphonate	785.2
100069	 OR	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(difluoromethyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(difluoromethyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7	649.3

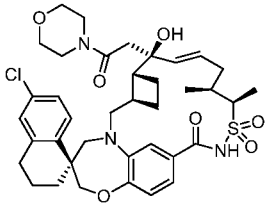
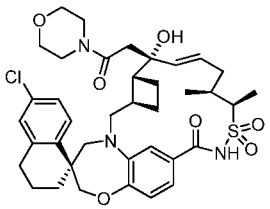
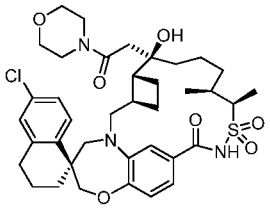
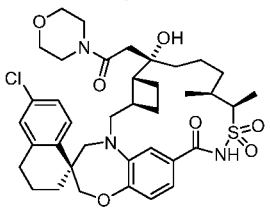
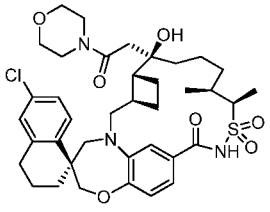
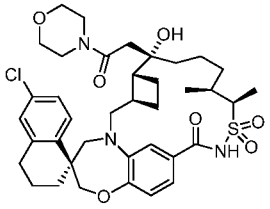
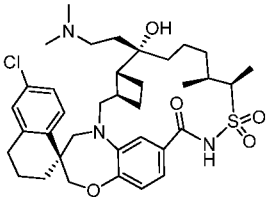
		.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100070	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(difluoromethyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(difluoromethyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	649.3
100071	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(difluoromethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(difluoromethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	663.0
100072	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((methylsulfonyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((methylsulfonyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	691.1

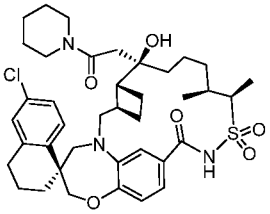
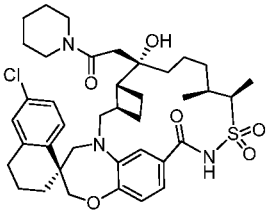
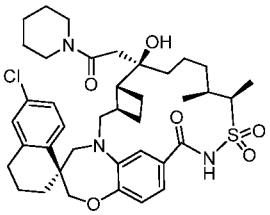
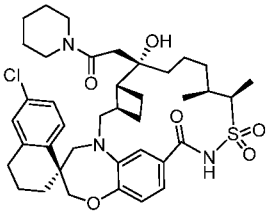
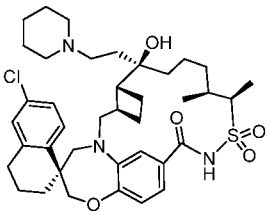
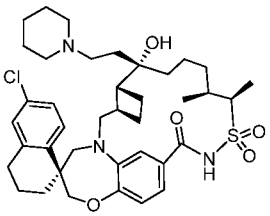
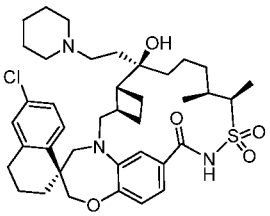
100073	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((methylsulfonyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((methylsulfonyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	691.0
100074	 AND  OR  AND 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(((S)-methylsulfinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(((R)-methylsulfinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(((S)-methylsulfinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(((R)-methylsulfinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	675.0
100075	 AND	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(((S)-methylsulfinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND	675.3

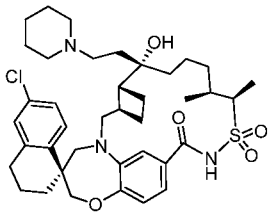
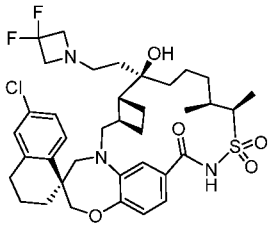
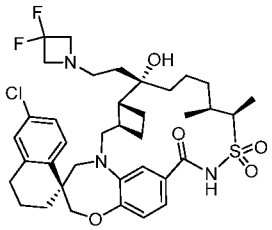
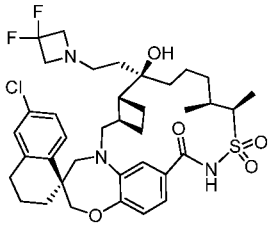
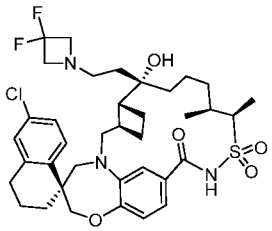
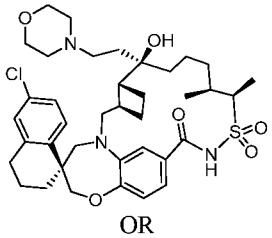
	 OR  AND 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(((R)-methylsulfinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(((S)-methylsulfinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(((R)-methylsulfinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100076	 OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-ethyl-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-ethyl-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	629.3
100077	 OR 	2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-dimethylacetamide OR 2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-dimethylacetamide	684.2

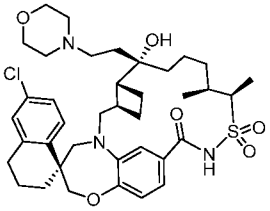
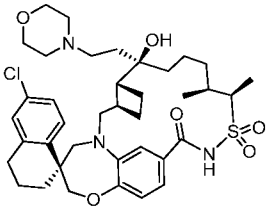
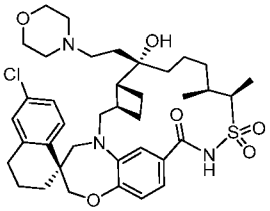
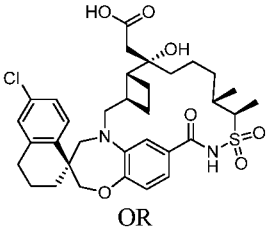
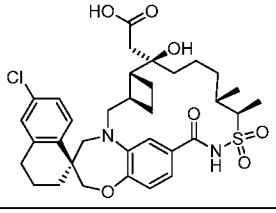
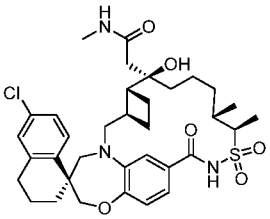
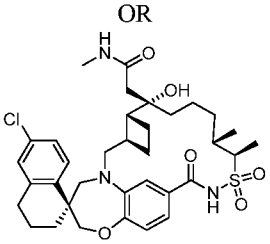
100078	 OR 	2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-dimethylacetamide OR 2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-dimethylacetamide	684.2
100079	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-ethyl-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-ethyl-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	629.1
100080	 OR 	((1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)acetonitrile OR ((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)acetonitrile	640.3
100081	 OR	((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)acetonitrile OR	640.3

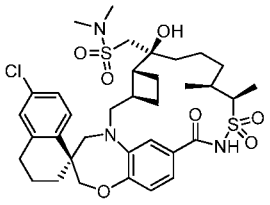
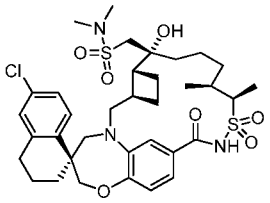
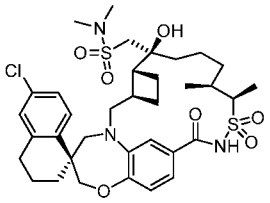
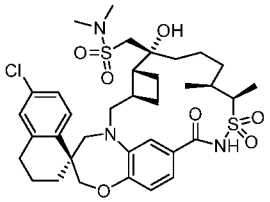
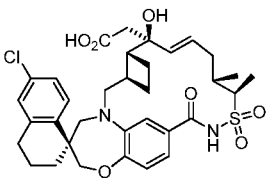
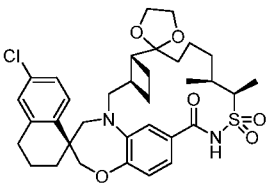
		((1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)acetonitrile	
100082		2-((1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N,N-dimethylacetamide	686.3
100083	 OR 	2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-diethylacetamide OR 2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-diethylacetamide	712.2
100084	 OR 	2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-diethylacetamide OR 2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-diethylacetamide	712.2

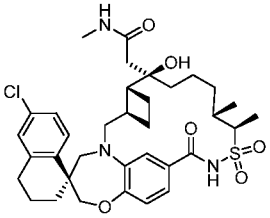
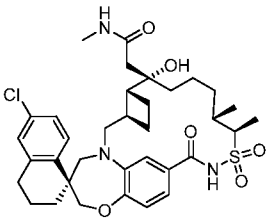
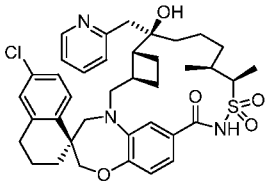
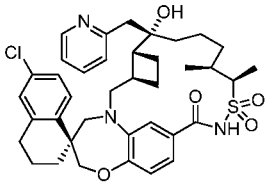
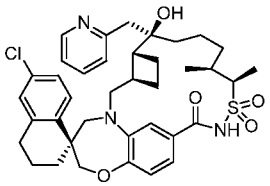
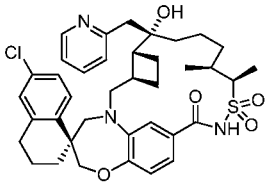
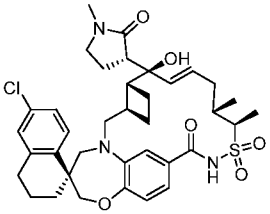
100085	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-(4-morpholinyl)-2-oxoethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-(4-morpholinyl)-2-oxoethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	726.1
100086	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-(4-morpholinyl)-2-oxoethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-(4-morpholinyl)-2-oxoethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	728.1
100087	 OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-(4-morpholinyl)-2-oxoethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-(4-morpholinyl)-2-oxoethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	728.1
100088		(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-(2-(dimethylamino)ethyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	672.3

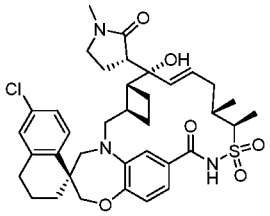
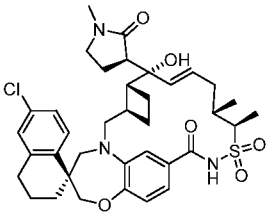
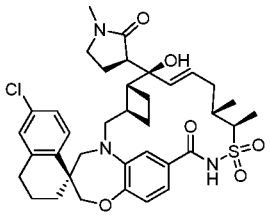
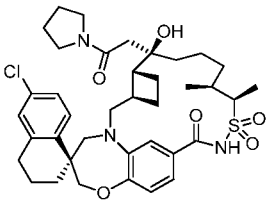
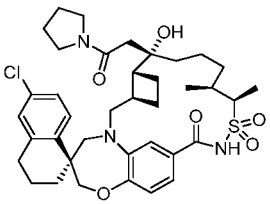
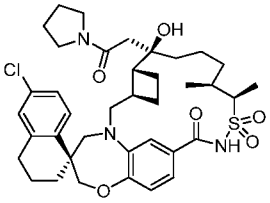
100089	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-oxo-2-(1-piperidinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-oxo-2-(1-piperidinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	726.3
100090	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-oxo-2-(1-piperidinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-oxo-2-(1-piperidinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	726.2
100091	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-(1-piperidinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-(1-piperidinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	712.2
100092		(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-(1-piperidinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	712.4

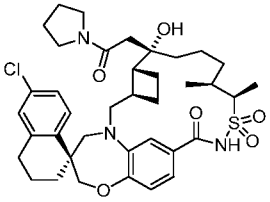
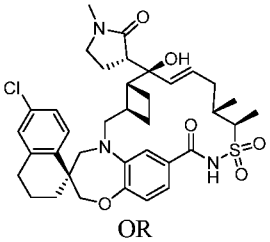
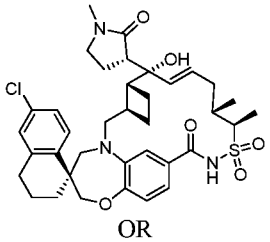
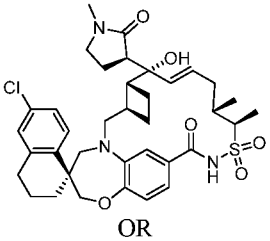
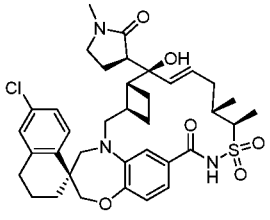
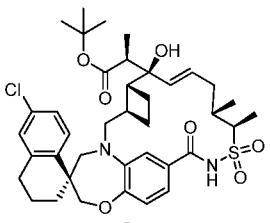
	OR 	OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-(1-piperidinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	
100093	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-(2-(3,3-difluoro-1-azetidinyl)ethyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-(2-(3,3-difluoro-1-azetidinyl)ethyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	720.2
100094	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-(2-(3,3-difluoro-1-azetidinyl)ethyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-(2-(3,3-difluoro-1-azetidinyl)ethyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	720.2
100095	 OR	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-(4-morpholinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-(4-morpholinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-	714.3

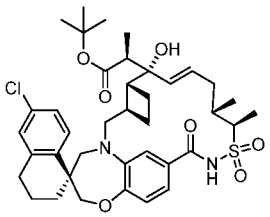
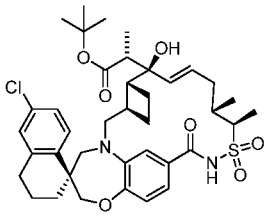
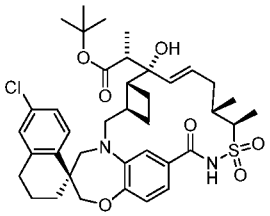
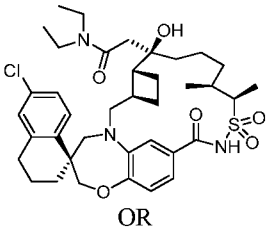
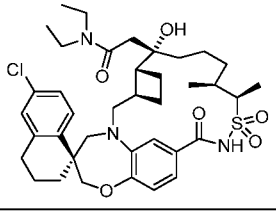
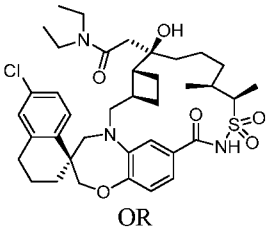
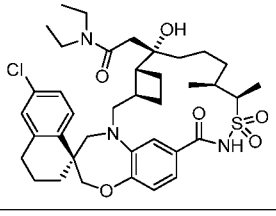
		[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	
100096	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-(4-morpholinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-(4-morpholinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	714.3
100097	 OR 	((1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)acetic acid OR ((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)acetic acid	658.8
100098	 OR 	2-((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N-methylacetamide OR 2-((1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N-methylacetamide	671.9

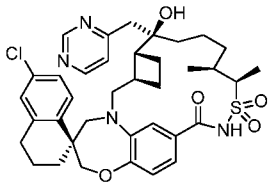
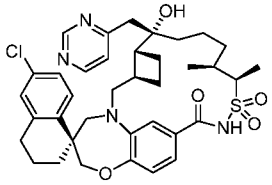
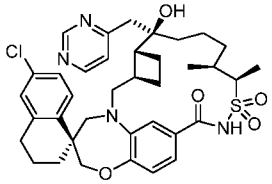
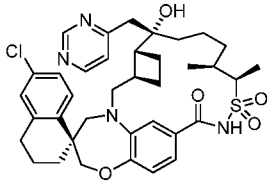
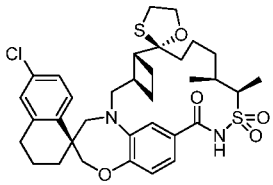
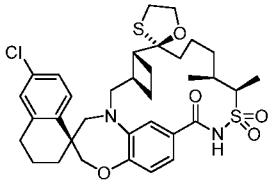
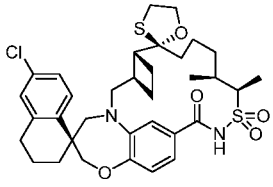
100099	 OR 	1-((1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N,N-dimethylmethanesulfonamide OR 1-((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N,N-dimethylmethanesulfonamide	722.2
100100	 OR 	1-((1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N,N-dimethylmethanesulfonamide OR 1-((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N,N-dimethylmethanesulfonamide	722.3
100101		((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetic acid	656.8
100102		(3'R,6'R,11'S,12'R,22'S)-6"-chloro-11',12'-dimethyl-3",4"-dihydro-2"H,15'H-dispiro[1,3-dioxolane-2,7'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-22',1"-naphthalen]-15'-one 13',13'-dioxide	643.3

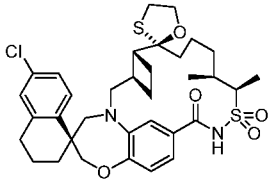
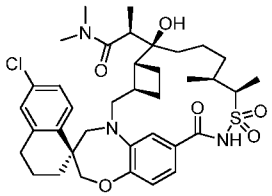
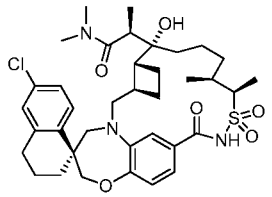
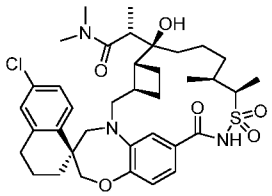
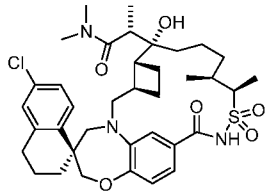
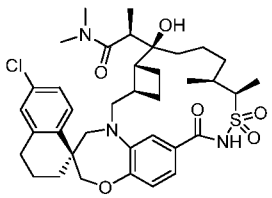
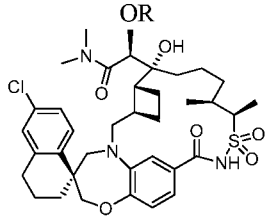
100103	 OR 	2-((1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N-methylacetamide OR 2-((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N-methylacetamide	671.9
100104	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-pyridinylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-pyridinylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	692.3
100105	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-pyridinylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-pyridinylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	692.3
100106		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((3S)-1-methyl-2-oxo-3-pyrrolidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	696.2

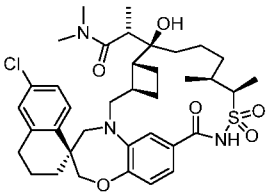
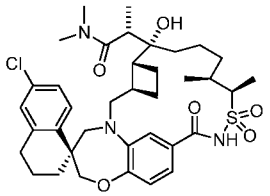
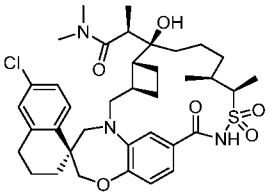
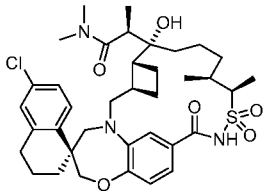
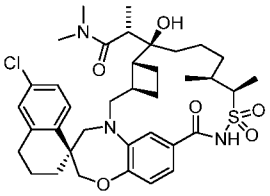
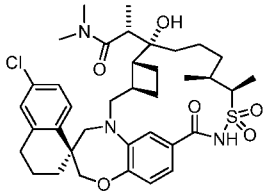
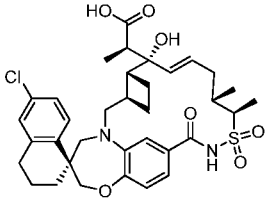
	OR  OR  OR 	OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((3R)-1-methyl-2-oxo-3-pyrrolidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((3S)-1-methyl-2-oxo-3-pyrrolidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((3R)-1-methyl-2-oxo-3-pyrrolidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100107	OR  OR 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-oxo-2-(1-pyrrolidinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-oxo-2-(1-pyrrolidinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	711.8
100108	 OR	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-oxo-2-(1-pyrrolidinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-oxo-2-(1-pyrrolidinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-	711.8

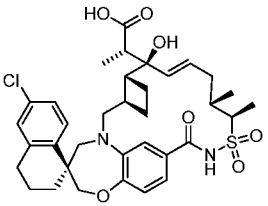
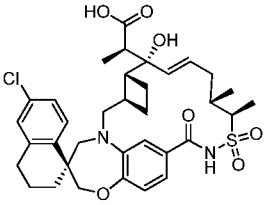
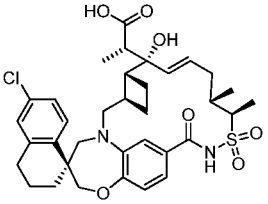
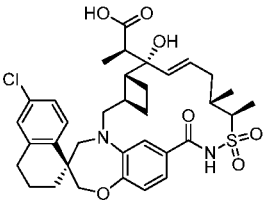
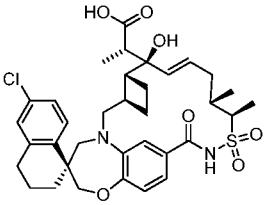
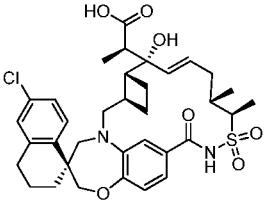
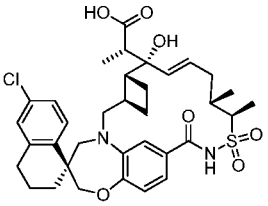
		[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	
100109	 OR  OR  OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((3S)-1-methyl-2-oxo-3-pyrrolidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((3R)-1-methyl-2-oxo-3-pyrrolidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((3S)-1-methyl-2-oxo-3-pyrrolidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((3R)-1-methyl-2-oxo-3-pyrrolidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	695.9
100110	 OR	2-methyl-2-propanyl (2R)-2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)propanoate OR 2-methyl-2-propanyl (2R)-2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-	726.8

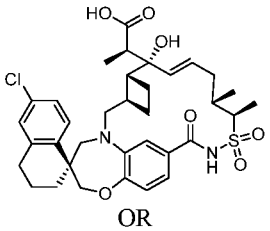
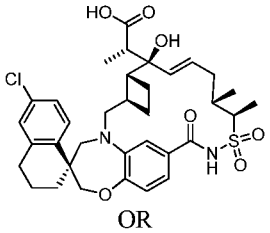
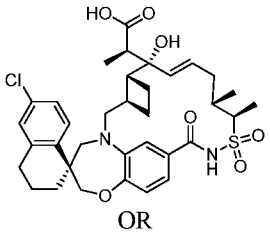
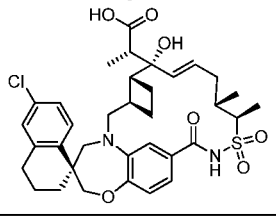
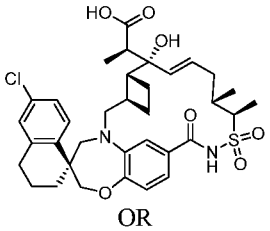
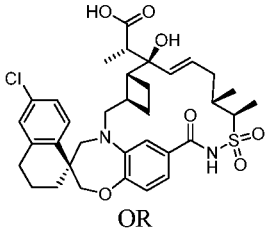
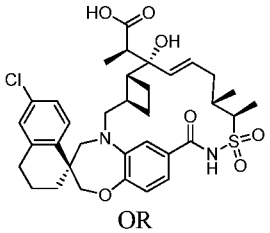
	 OR  OR 	dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)propanoate OR 2-methyl-2-propanyl (2S)-2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)propanoate OR 2-methyl-2-propanyl (2S)-2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)propanoate	
100111	 OR 	2-((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N,N-diethylacetamide OR 2-((1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N,N-diethylacetamide	713.9
100112	 OR 	2-((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N,N-diethylacetamide OR 2-((1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N,N-diethylacetamide	713.9

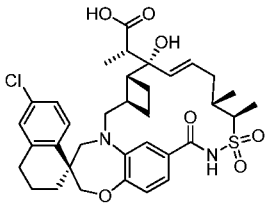
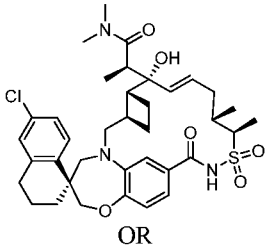
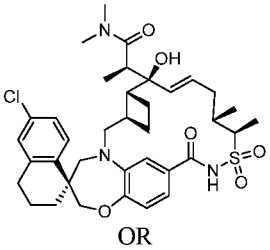
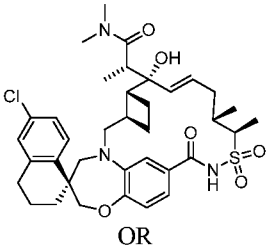
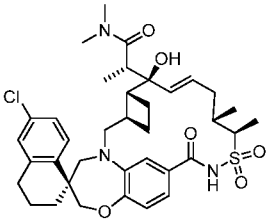
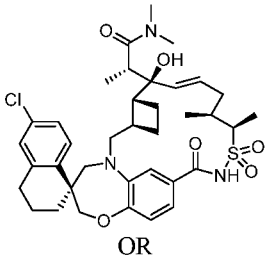
100113	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(4-pyrimidinylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(4-pyrimidinylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	693.3
100114	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(4-pyrimidinylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(4-pyrimidinylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	693.3
100115	 OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',2"-[1,3]oxathiolan]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',2"-[1,3]oxathiolan]-15'-one 13',13'-dioxide	659.3
100116	 OR	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',2"-[1,3]oxathiolan]-15'-one 13',13'-dioxide OR	659.3

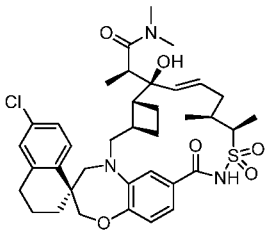
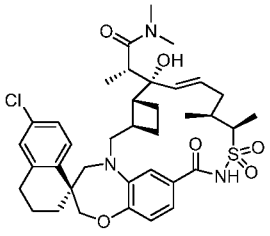
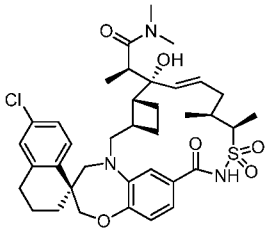
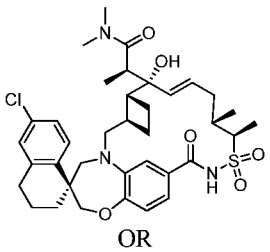
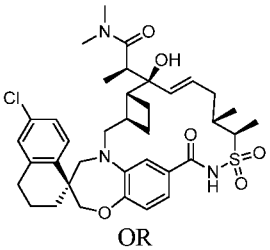
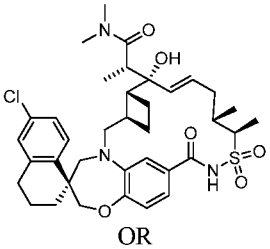
		(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',2"-[1,3]oxathiolan]-15'-one 13',13'-dioxide	
100117	 OR  OR  OR 	(2R)-2-((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N,N-dimethylpropanamide OR (2R)-2-((1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N,N-dimethylpropanamide OR (2S)-2-((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N,N-dimethylpropanamide OR (2S)-2-((1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N,N-dimethylpropanamide	700.4
100118	 OR  OR	(2R)-2-((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N,N-dimethylpropanamide OR (2R)-2-((1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N,N-dimethylpropanamide OR	700.4

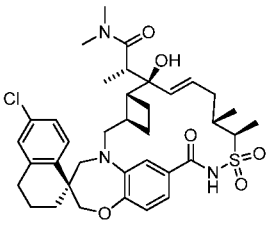
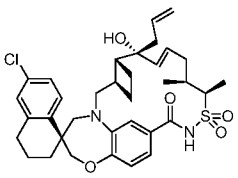
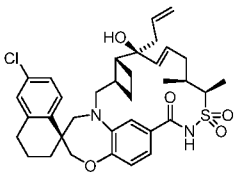
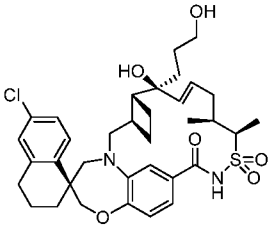
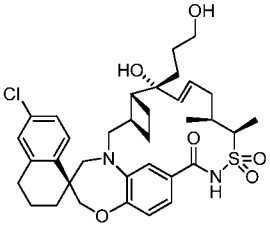
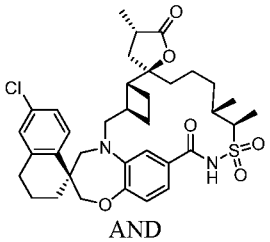
	 OR 	(2S)-2-((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N,N-dimethylpropanamide OR (2S)-2-((1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N,N-dimethylpropanamide	
100119	 OR  OR  OR 	(2R)-2-((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N,N-dimethylpropanamide OR (2R)-2-((1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N,N-dimethylpropanamide OR (2S)-2-((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N,N-dimethylpropanamide OR (2S)-2-((1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N,N-dimethylpropanamide	700.4
100120	 OR	(2S)-2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)propanoic acid OR	670.8

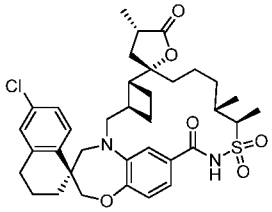
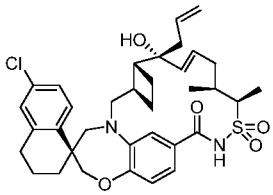
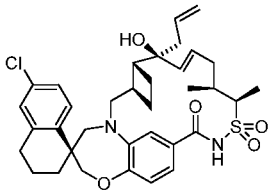
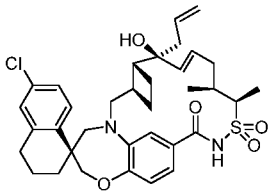
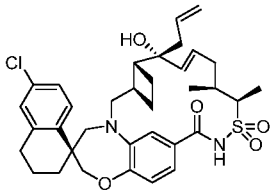
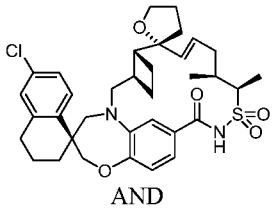
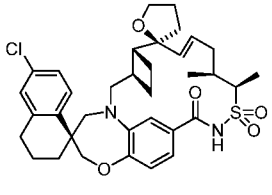
	 OR  OR 	(2R)-2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)propanoic acid OR (2S)-2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)propanoic acid OR (2R)-2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)propanoic acid	
100121	 OR  OR  OR 	(2S)-2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)propanoic acid OR (2R)-2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)propanoic acid OR (2S)-2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)propanoic acid OR (2R)-2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)propanoic acid	670.8

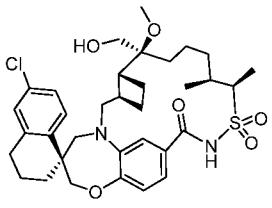
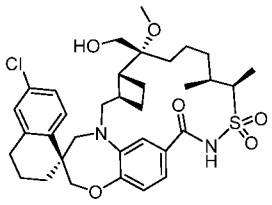
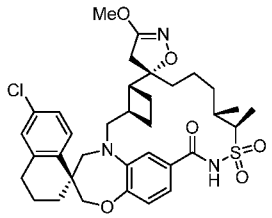
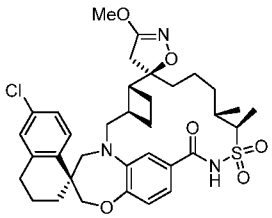
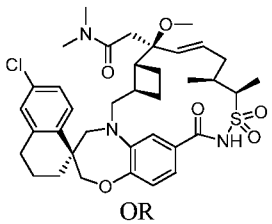
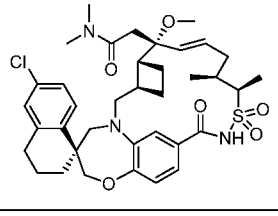
100122	 OR  OR  OR 	(2S)-2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)propanoic acid OR (2R)-2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)propanoic acid OR (2S)-2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)propanoic acid OR (2R)-2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)propanoic acid	670.8
100123	 OR  OR  OR	(2S)-2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)propanoic acid OR (2R)-2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)propanoic acid OR (2S)-2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)propanoic acid OR	670.8

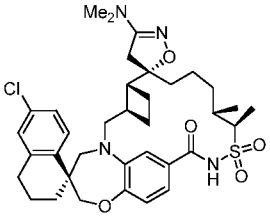
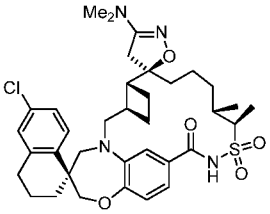
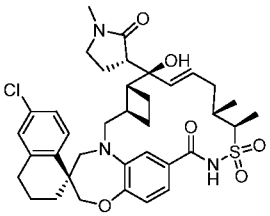
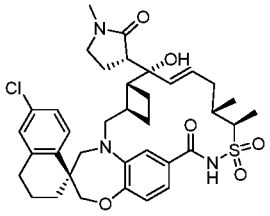
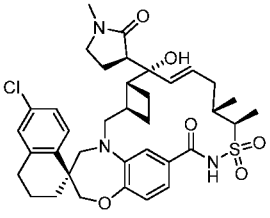
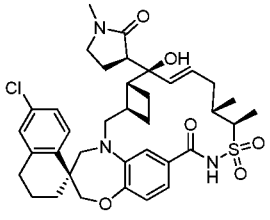
		(2R)-2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)propanoic acid	
100124	 OR  OR  OR 	(2R)-2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-dimethylpropanamide OR (2S)-2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-dimethylpropanamide OR (2R)-2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-dimethylpropanamide OR (2S)-2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-dimethylpropanamide	697.7
100125	 OR	(2S)-2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-dimethylpropanamide OR (2R)-2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-	698.2

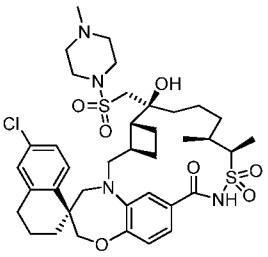
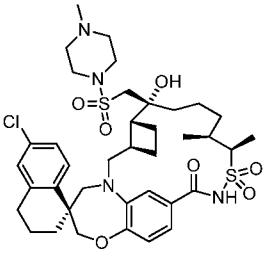
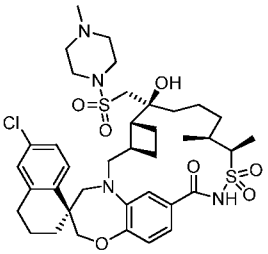
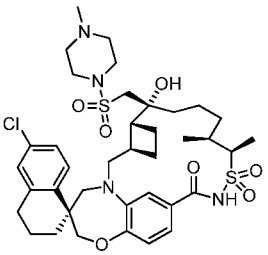
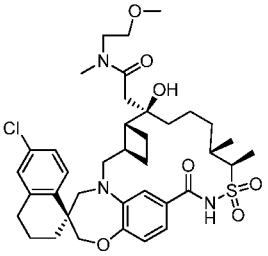
	 OR  OR 	spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-dimethylpropanamide OR (2S)-2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-dimethylpropanamide OR (2R)-2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-dimethylpropanamide	
100126	 OR  OR  OR	(2R)-2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-dimethylpropanamide OR (2S)-2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-dimethylpropanamide OR (2R)-2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-dimethylpropanamide OR (2S)-2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-	698.2

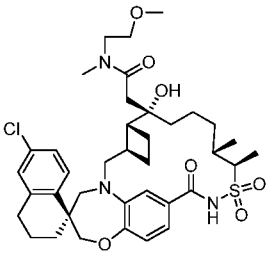
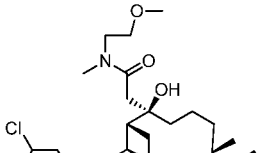
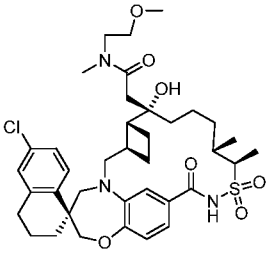
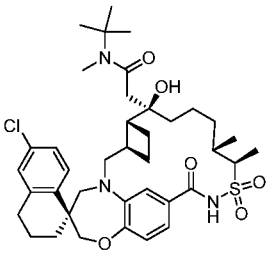
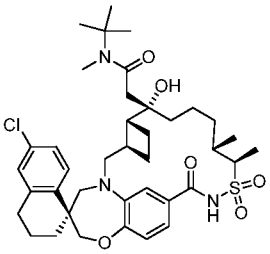
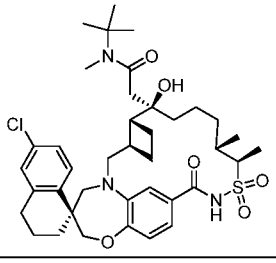
		13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-dimethylpropanamide	
100127	 AND 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-propen-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-propen-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	639.3
100128	 AND 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(3-hydroxypropyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(3-hydroxypropyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	657.4
100129	 AND	(2S,3'R,4S,6'R,11'S,12'R,22'S)-6"-chloro-4,11',12'-trimethyl-3,3",4,4"-tetrahydro-2"H,5H,15'H-dispiro[furan-2,7'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-22',1"-naphthalene]-5,15'-dione 13',13'-dioxide AND (2R,3'R,4S,6'R,11'S,12'R,22'S)-6"-chloro-4,11',12'-trimethyl-3,3",4,4"-tetrahydro-2"H,5H,15'H-dispiro[furan-2,7'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-22',1"-naphthalene]-5,15'-dione 13',13'-dioxide	669.2

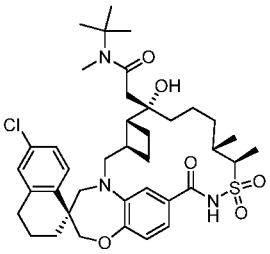
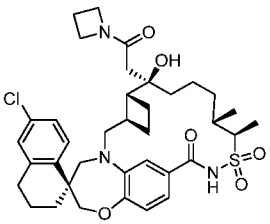
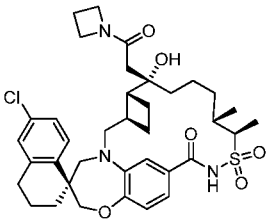
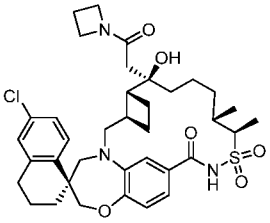
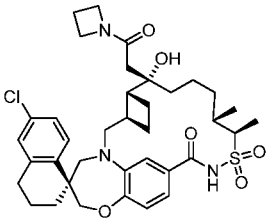
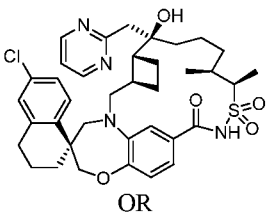
			
100130	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-propen-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-propen-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	639.0
100131	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-propen-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-propen-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	639.2
100132	 AND 	(2S,3'R,6'R,8'E,11'S,12'R,22'S)-6"-chloro-11',12'-dimethyl-3",4,4",5-tetrahydro-2"H,3H,15'H-dispiro[furan-2,7'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-22',1"-naphthalen]-15'-one 13',13'-dioxide AND (2R,3'R,6'R,8'E,11'S,12'R,22'S)-6"-chloro-11',12'-dimethyl-3",4,4",5-tetrahydro-2"H,3H,15'H-dispiro[furan-2,7'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24	639.3

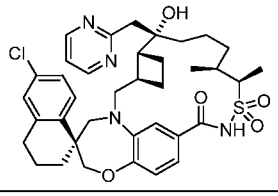
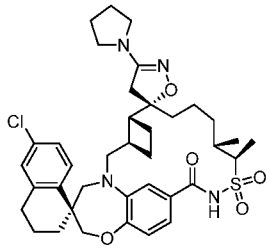
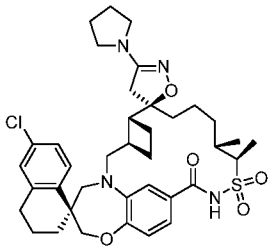
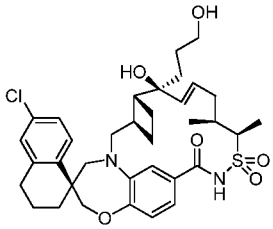
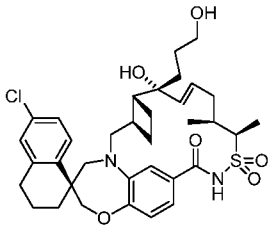
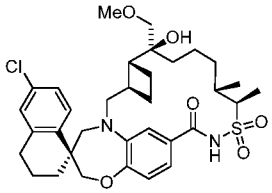
		]tetraene-22',1"-naphthalen]-15'-one 13',13'-dioxide	
100133	 OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-(hydroxymethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-(hydroxymethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	645.2
100134	 OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-3"-methoxy-11',12'-dimethyl-3,4-dihydro-2H,4"H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',5"-[1,2]oxazol]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-3"-methoxy-11',12'-dimethyl-3,4-dihydro-2H,4"H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',5"-[1,2]oxazol]-15'-one 13',13'-dioxide	670.1
100135	 OR 	2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-dimethylacetamide OR 2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-dimethylacetamide	720.2

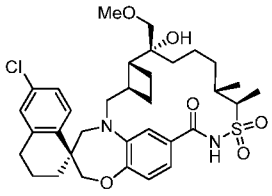
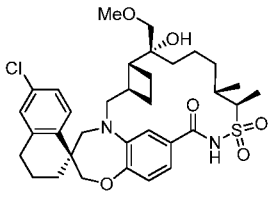
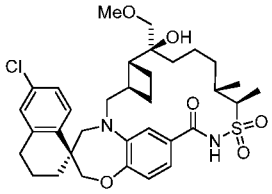
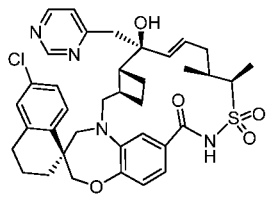
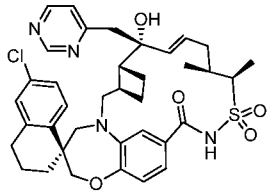
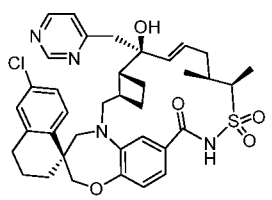
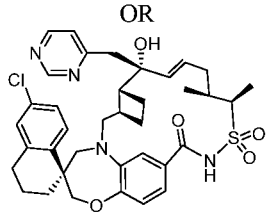
100136	 OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-3"-(dimethylamino)-11',12'-dimethyl-3,4-dihydro-2H,4"H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',5"-[1,2]oxazol]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-3"-(dimethylamino)-11',12'-dimethyl-3,4-dihydro-2H,4"H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',5"-[1,2]oxazol]-15'-one 13',13'-dioxide	683.2
100137	 OR  OR  OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((3S)-1-methyl-2-oxo-3-pyrrolidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((3R)-1-methyl-2-oxo-3-pyrrolidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((3S)-1-methyl-2-oxo-3-pyrrolidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((3R)-1-methyl-2-oxo-3-pyrrolidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	696.2

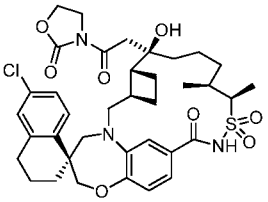
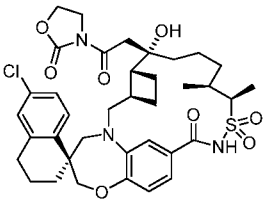
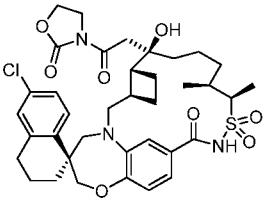
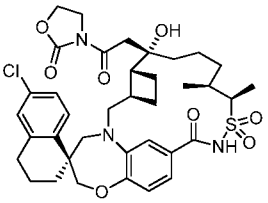
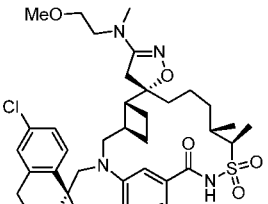
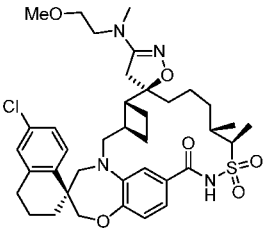
100138	 OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(((4-methyl-1-piperazinyl)sulfonyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(((4-methyl-1-piperazinyl)sulfonyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	777.2
100139	 OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(((4-methyl-1-piperazinyl)sulfonyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(((4-methyl-1-piperazinyl)sulfonyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	777.2
100140	 OR	2-((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N-(2-methoxyethyl)-N-methylacetamide OR 2-((1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N-(2-methoxyethyl)-N-methylacetamide	730.2

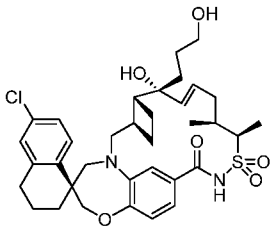
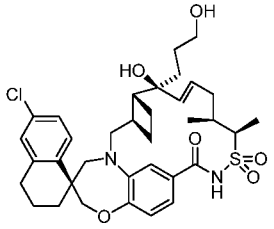
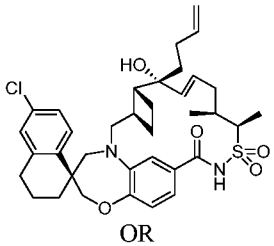
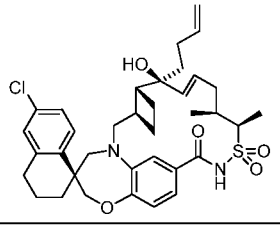
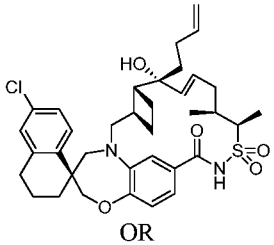
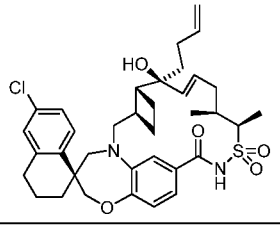
			
100141	 OR 	2-((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N-(2-methoxyethyl)-N-methylacetamide OR 2-((1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N-(2-methoxyethyl)-N-methylacetamide	730.2
100142	 OR 	2-((1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N-methyl-N-(2-methyl-2-propanyl)acetamide OR 2-((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N-methyl-N-(2-methyl-2-propanyl)acetamide	728.3
100143		2-((1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N-methyl-N-(2-methyl-2-propanyl)acetamide	728.2

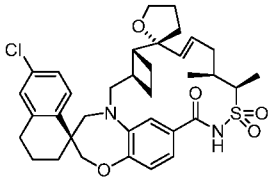
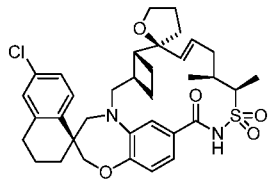
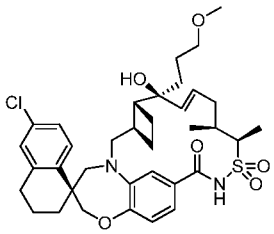
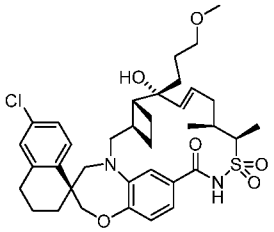
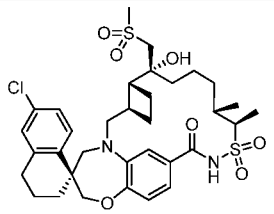
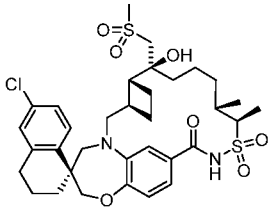
	 OR	OR 2-((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N-methyl-N-(2-methyl-2-propanyl)acetamide	
100144	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-7'-(2-(1-azetidinyl)-2-oxoethyl)-6-chloro-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-7'-(2-(1-azetidinyl)-2-oxoethyl)-6-chloro-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	698.5
100145	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-7'-(2-(1-azetidinyl)-2-oxoethyl)-6-chloro-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-7'-(2-(1-azetidinyl)-2-oxoethyl)-6-chloro-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	698.5
100146	 OR	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-pyrimidinylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-pyrimidinylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-	693.2

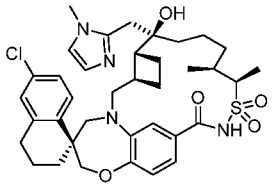
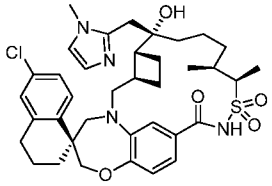
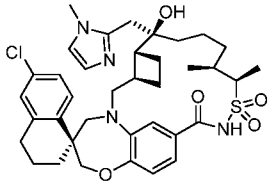
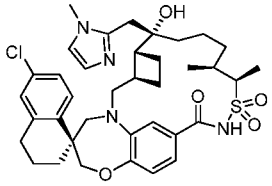
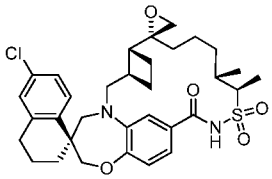
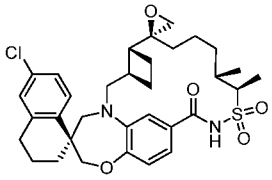
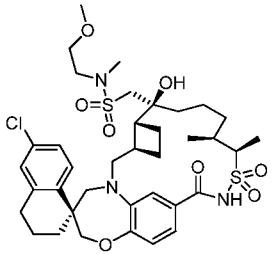
		[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene]-15'-one 13',13'-dioxide	
100147	 OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-11',12'-dimethyl-3"-(1-pyrrolidinyl)-3,4-dihydro-2H,4"H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',5"-[1,2]oxazol]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-11',12'-dimethyl-3"-(1-pyrrolidinyl)-3,4-dihydro-2H,4"H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',5"-[1,2]oxazol]-15'-one 13',13'-dioxide	709.1
100148	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(3-hydroxypropyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(3-hydroxypropyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	657.3
100149	 OR	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-7'-(methoxymethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-7'-(methoxymethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7	645.2

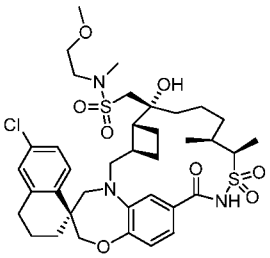
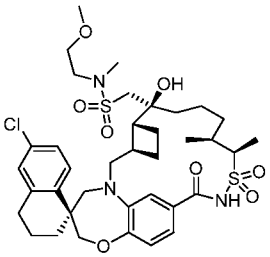
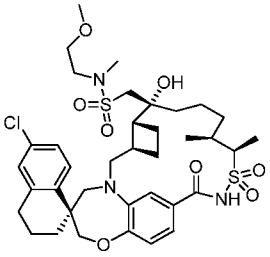
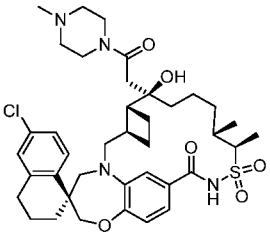
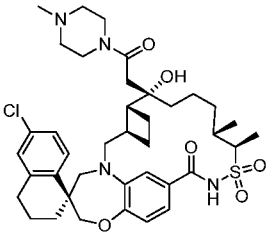
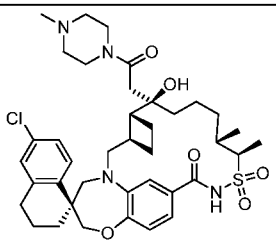
		.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	
100150	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-7'-(methoxymethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-7'-(methoxymethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	645.2
100151	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(4-pyrimidinylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(4-pyrimidinylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	691.2
100152	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(4-pyrimidinylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(4-pyrimidinylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	691.2

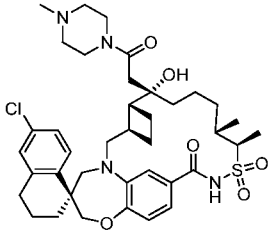
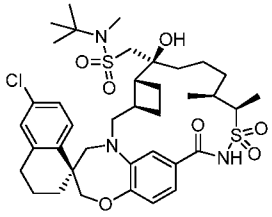
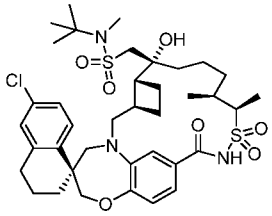
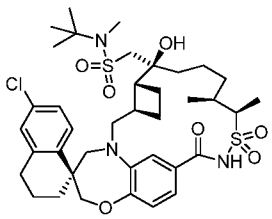
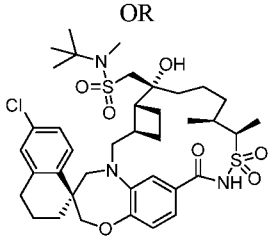
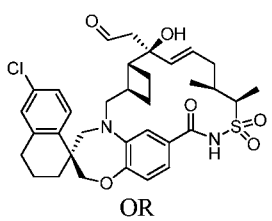
100153	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-oxo-2-(2-oxo-1,3-oxazolidin-3-yl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-oxo-2-(2-oxo-1,3-oxazolidin-3-yl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	728.5
100154	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-oxo-2-(2-oxo-1,3-oxazolidin-3-yl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-oxo-2-(2-oxo-1,3-oxazolidin-3-yl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	728.5
100155	 OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-3"-((2-methoxyethyl)(methyl)amino)-11',12'-dimethyl-3,4-dihydro-2H,4"H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',5"-[1,2]oxazol]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-3"-((2-methoxyethyl)(methyl)amino)-11',12'-dimethyl-3,4-dihydro-2H,4"H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',5"-[1,2]oxazol]-15'-one 13',13'-dioxide	727.1

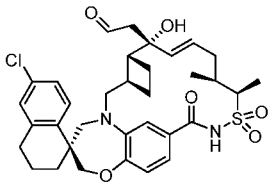
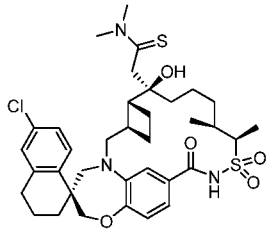
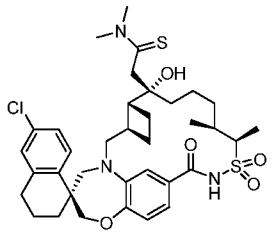
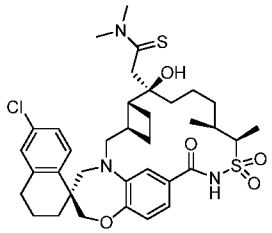
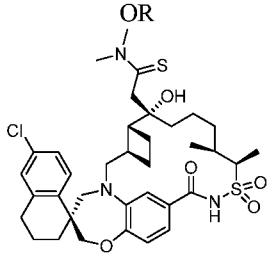
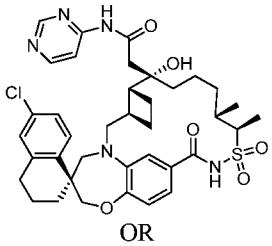
100156	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(3-hydroxypropyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(3-hydroxypropyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	657.3
100157	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-7'-(3-buten-1-yl)-6-chloro-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-7'-(3-buten-1-yl)-6-chloro-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	653.0
100158	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-7'-(3-buten-1-yl)-6-chloro-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-7'-(3-buten-1-yl)-6-chloro-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	653.0

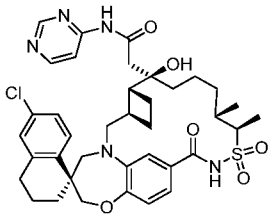
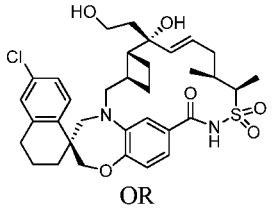
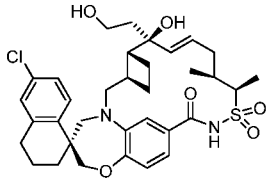
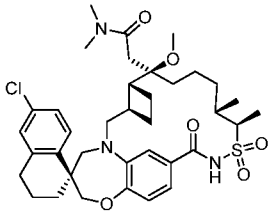
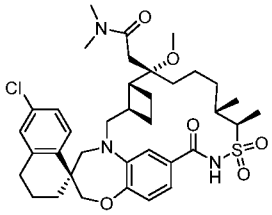
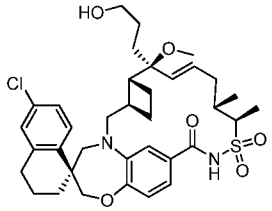
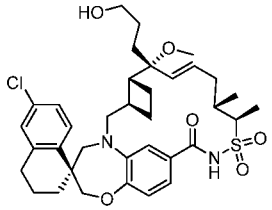
100159	 OR 	(2S,3'R,6'R,8'E,11'S,12'R,22'S)-6"-chloro-11',12'-dimethyl-3",4,4",5-tetrahydro-2"H,3H,15'H-dispiro[furan-2,7'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-22',1"-naphthalen]-15'-one 13',13'-dioxide OR (2R,3'R,6'R,8'E,11'S,12'R,22'S)-6"-chloro-11',12'-dimethyl-3",4,4",5-tetrahydro-2"H,3H,15'H-dispiro[furan-2,7'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-22',1"-naphthalen]-15'-one 13',13'-dioxide	639.3
100160	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(3-methoxypropyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(3-methoxypropyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	671.4
100161	 AND 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((methylsulfonyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((methylsulfonyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	693.2

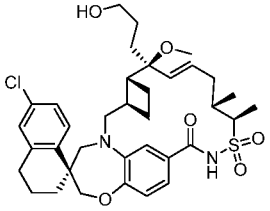
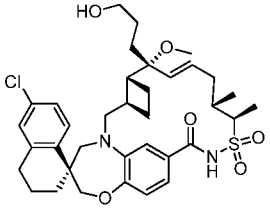
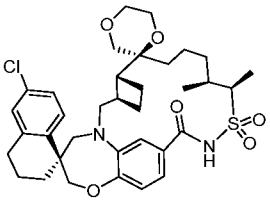
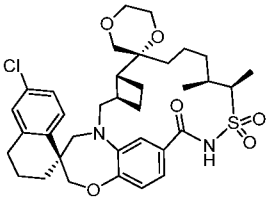
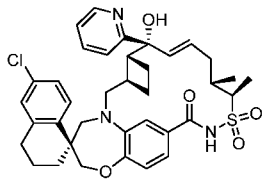
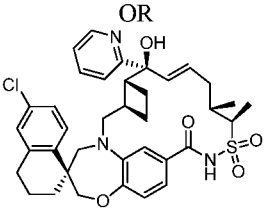
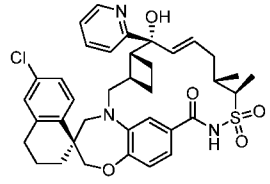
100162	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((1-methyl-1H-imidazol-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((1-methyl-1H-imidazol-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	695.5
100163	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((1-methyl-1H-imidazol-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((1-methyl-1H-imidazol-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	695.5
100164	 AND 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',2"-oxiran]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',2"-oxiran]-15'-one 13',13'-dioxide	613.2
100165	 OR	1-((1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N-(2-methoxyethyl)-N-methylmethanesulfonamide OR	766.2

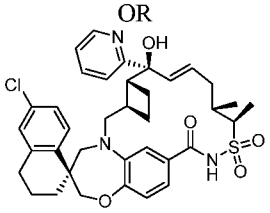
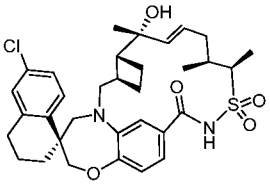
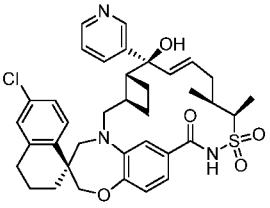
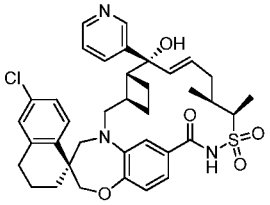
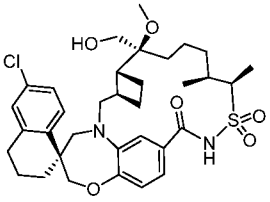
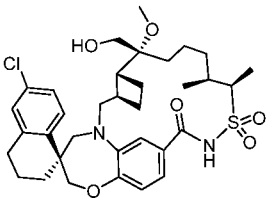
		1-((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N-(2-methoxyethyl)-N-methylmethanesulfonamide	
100166	 OR 	1-((1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N-(2-methoxyethyl)-N-methylmethanesulfonamide OR 1-((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N-(2-methoxyethyl)-N-methylmethanesulfonamide	766.3
100167	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-(4-methyl-1-piperazinyl)-2-oxoethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-(4-methyl-1-piperazinyl)-2-oxoethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	741.2
100168	 OR	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-(4-methyl-1-piperazinyl)-2-oxoethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR	741.2

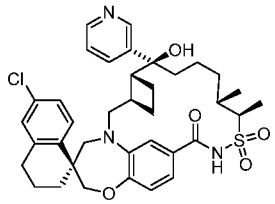
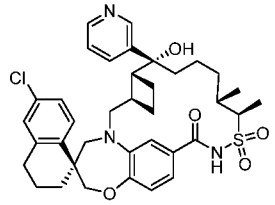
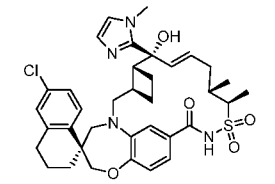
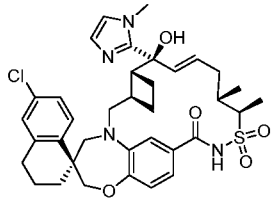
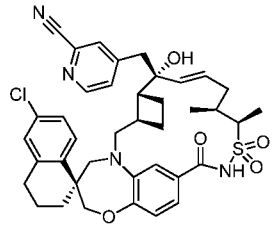
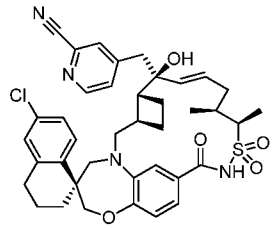
		(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-(4-methyl-1-piperazinyl)-2-oxoethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	
100169	 OR 	1-((1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N-methyl-N-(2-methyl-2-propanyl)methanesulfonamide OR 1-((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N-methyl-N-(2-methyl-2-propanyl)methanesulfonamide	764.2
100170	 OR 	1-((1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N-methyl-N-(2-methyl-2-propanyl)methanesulfonamide OR 1-((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N-methyl-N-(2-methyl-2-propanyl)methanesulfonamide	764.2
100171	 OR	((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetaldehyde OR ((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-	641.5

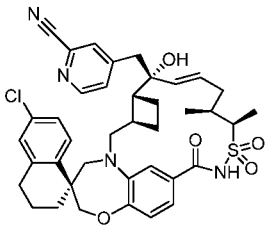
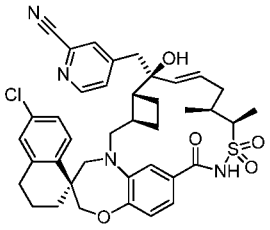
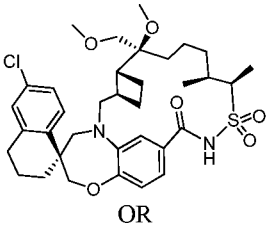
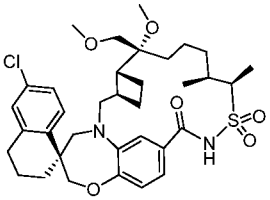
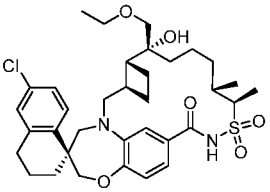
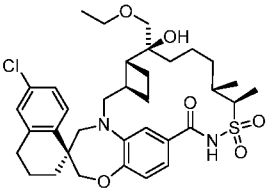
		[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetaldehyde	
100172	 OR 	((1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N,N-dimethylethanethioamide OR ((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N,N-dimethylethanethioamide	702.1
100173	 OR 	((1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N,N-dimethylethanethioamide OR ((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N,N-dimethylethanethioamide	702.1
100174	 OR	2-((1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N-4-pyrimidinylacetamide OR 2-((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7	736.2

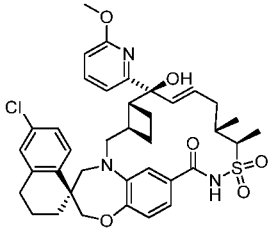
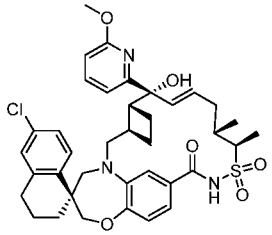
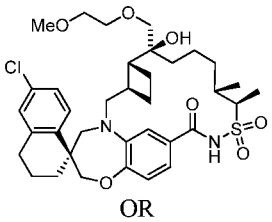
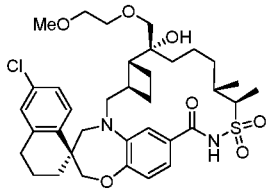
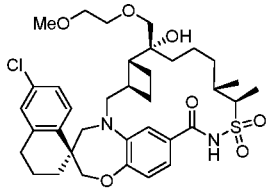
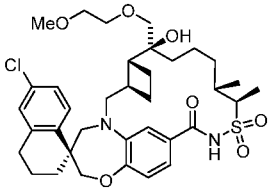
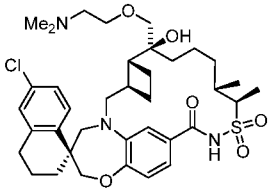
		.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N-4-pyrimidinylacetamide	
100175	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(2-hydroxyethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(2-hydroxyethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	643.4
100176	 OR 	2-((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N,N-dimethylacetamide OR 2-((1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)-N,N-dimethylacetamide	700.2
100177	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(3-hydroxypropyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(3-hydroxypropyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	671.2

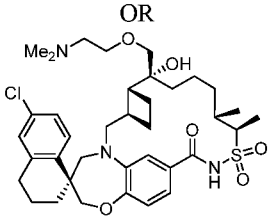
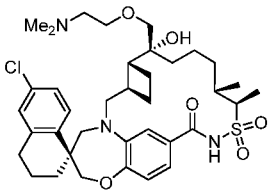
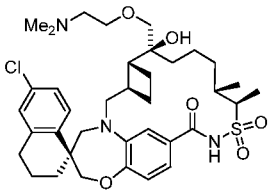
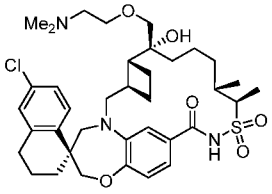
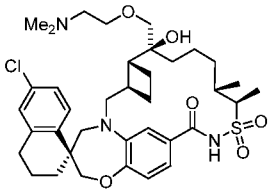
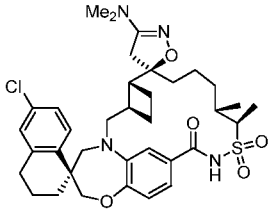
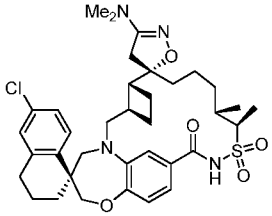
100178	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(3-hydroxypropyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(3-hydroxypropyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	671.0
100179	 OR 	(2S,3'R,6'R,11'S,12'R,22'S)-6"-chloro-11',12'-dimethyl-3",4"-dihydro-2"H,15'H-dispiro[1,4-dioxane-2,7'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-22',1"-naphthalen]-15'-one 13',13'-dioxide OR (2R,3'R,6'R,11'S,12'R,22'S)-6"-chloro-11',12'-dimethyl-3",4"-dihydro-2"H,15'H-dispiro[1,4-dioxane-2,7'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-22',1"-naphthalen]-15'-one 13',13'-dioxide	657.2
100180	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	676.0
100181		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7	676.0

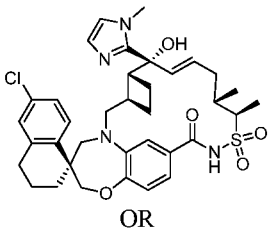
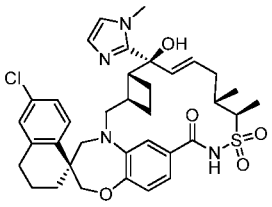
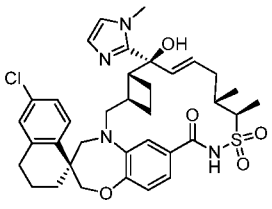
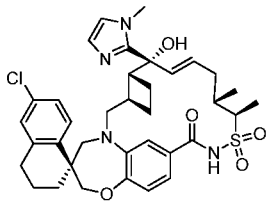
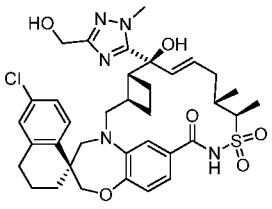
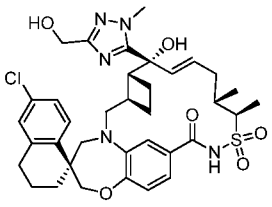
	OR 	.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100182		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	613.1
100183	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(3-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(3-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	676.2
100184	 OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-(hydroxymethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-(hydroxymethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	645.2

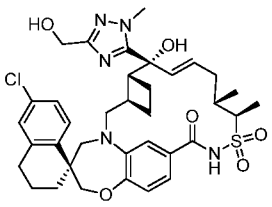
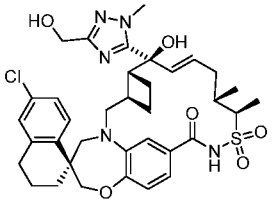
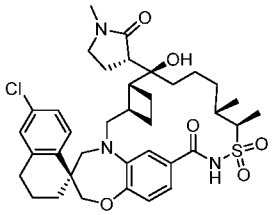
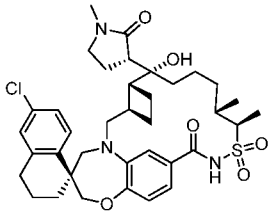
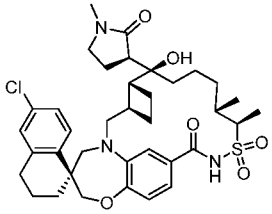
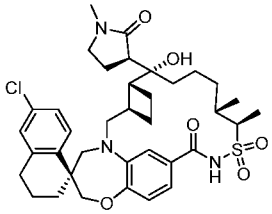
100185	 OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(3-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(3-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	678.2
100186	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(1-methyl-1H-imidazol-2-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(1-methyl-1H-imidazol-2-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	679.2
100187	 OR 	4-(((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)methyl)-2-pyridinecarbonitrile OR 4-(((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)methyl)-2-pyridinecarbonitrile	715.3

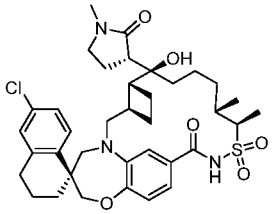
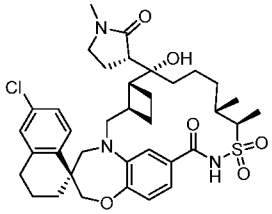
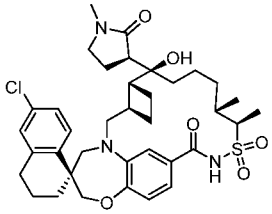
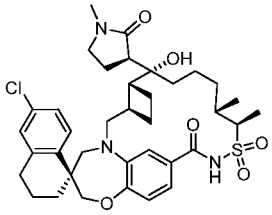
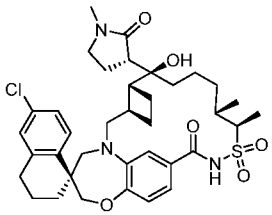
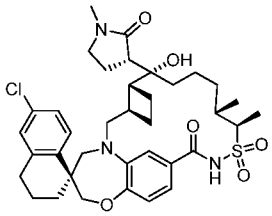
100188	 OR 	4-(((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)methyl)-2-pyridinecarbonitrile OR 4-(((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)methyl)-2-pyridinecarbonitrile	715.3
100189	 OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-methoxy-7'-(methoxymethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-methoxy-7'-(methoxymethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	659.2
100190	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-(ethoxymethyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-(ethoxymethyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	659.2

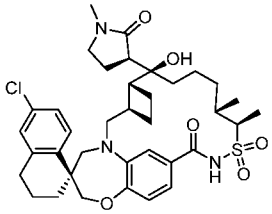
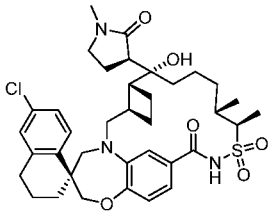
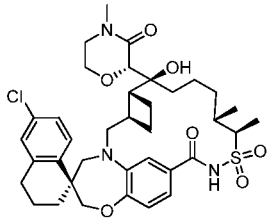
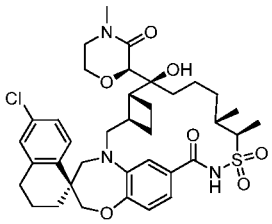
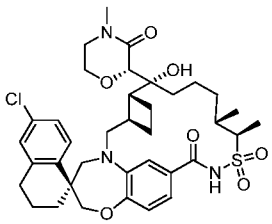
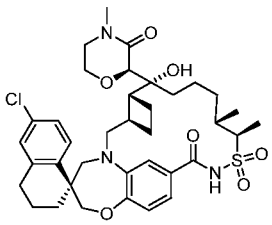
100191	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(6-methoxy-2-pyridinyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(6-methoxy-2-pyridinyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	706.2
100192	 OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-7'-((2-methoxyethoxy)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-7'-((2-methoxyethoxy)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	689.2
100193	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-7'-((2-methoxyethoxy)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-7'-((2-methoxyethoxy)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	689.2
100194		(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-((2-(dimethylamino)ethoxy)methyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	702.2

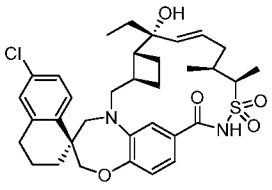
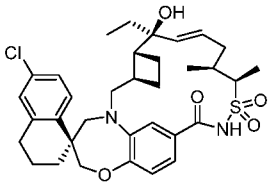
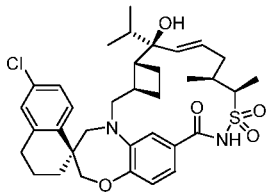
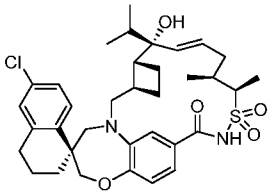
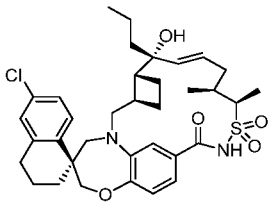
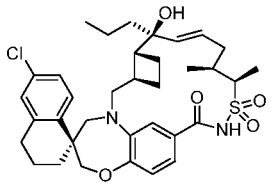
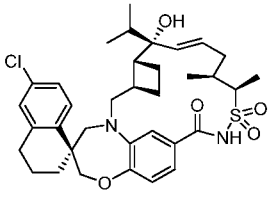
	OR 	OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-((2-(dimethylamino)ethoxy)methyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	
100195	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-((2-(dimethylamino)ethoxy)methyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-((2-(dimethylamino)ethoxy)methyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	702.2
100196	 AND 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-((2-(dimethylamino)ethoxy)methyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-((2-(dimethylamino)ethoxy)methyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	702.2
100197	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-3"-(dimethylamino)-11',12'-dimethyl-3,4-dihydro-2H,4"H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',5"-[1,2]oxazol]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-3"-(dimethylamino)-11',12'-dimethyl-3,4-dihydro-2H,4"H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]t	683.2

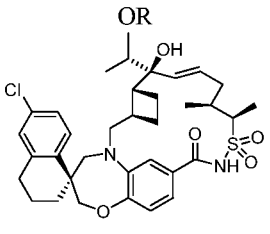
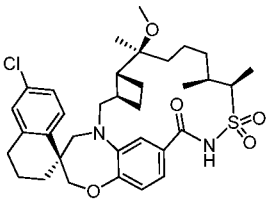
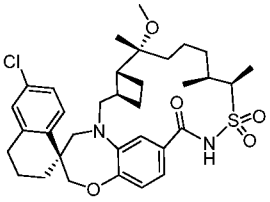
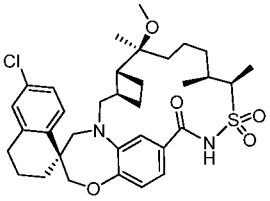
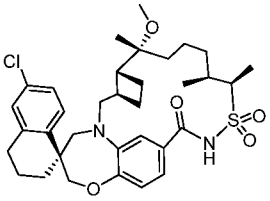
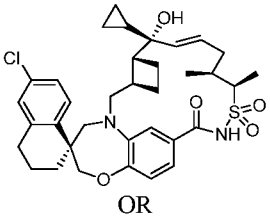
		riene-7',5"-[1,2]oxazol]-15'-one 13',13'-dioxide	
100198	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(1-methyl-1H-imidazol-2-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(1-methyl-1H-imidazol-2-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	679.2
100199	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(1-methyl-1H-imidazol-2-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(1-methyl-1H-imidazol-2-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	679.2
100200	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(3-(hydroxymethyl)-1-methyl-1H-1,2,4-triazol-5-yl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(3-(hydroxymethyl)-1-methyl-1H-1,2,4-triazol-5-yl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	710.2

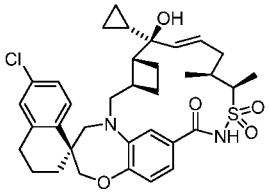
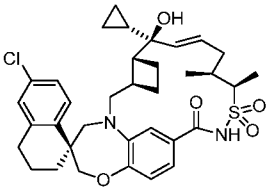
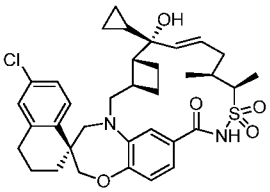
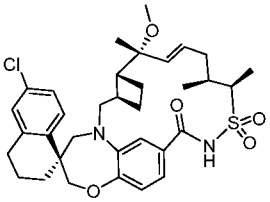
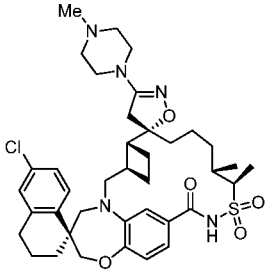
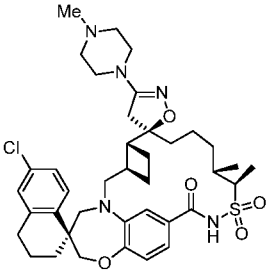
100201	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(3-(hydroxymethyl)-1-methyl-1H-1,2,4-triazol-5-yl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(3-(hydroxymethyl)-1-methyl-1H-1,2,4-triazol-5-yl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	710.2
100202	 OR  OR  OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((3S)-1-methyl-2-oxo-3-pyrrolidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((3S)-1-methyl-2-oxo-3-pyrrolidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((3R)-1-methyl-2-oxo-3-pyrrolidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((3R)-1-methyl-2-oxo-3-pyrrolidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	698.1

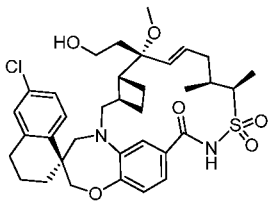
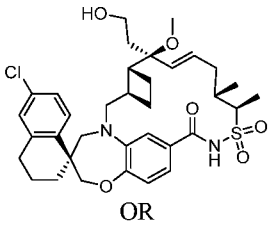
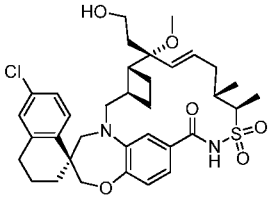
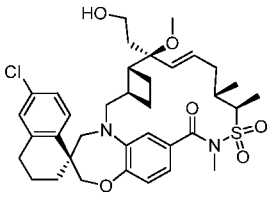
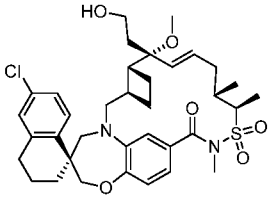
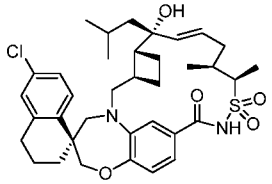
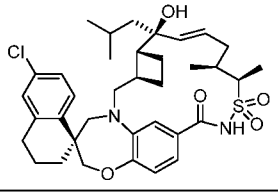
100203	 OR  OR  OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((3S)-1-methyl-2-oxo-3-pyrrolidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((3S)-1-methyl-2-oxo-3-pyrrolidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((3R)-1-methyl-2-oxo-3-pyrrolidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((3R)-1-methyl-2-oxo-3-pyrrolidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	698.2
100204	 OR  OR	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((3S)-1-methyl-2-oxo-3-pyrrolidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((3S)-1-methyl-2-oxo-3-pyrrolidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((3R)-1-methyl-2-oxo-3-pyrrolidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-	698.1

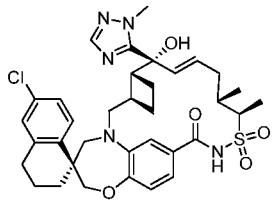
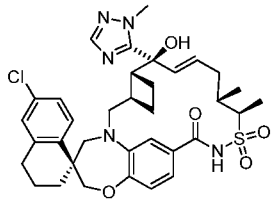
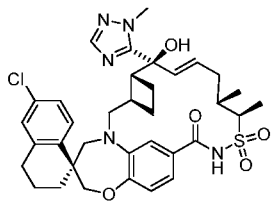
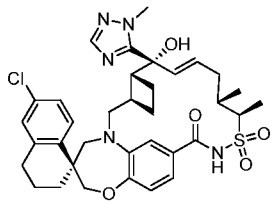
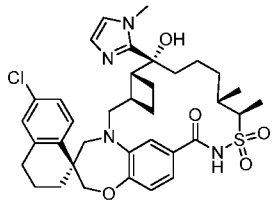
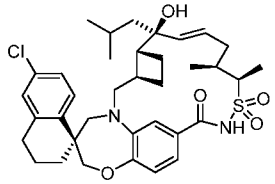
	 OR 	[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((3R)-1-methyl-2-oxo-3-pyrrolidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	
100205	 OR  OR  OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((2S)-4-methyl-3-oxo-2-morpholinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((2R)-4-methyl-3-oxo-2-morpholinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((2S)-4-methyl-3-oxo-2-morpholinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((2R)-4-methyl-3-oxo-2-morpholinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	714.1

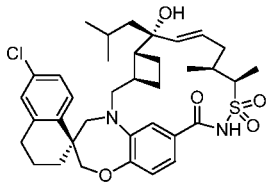
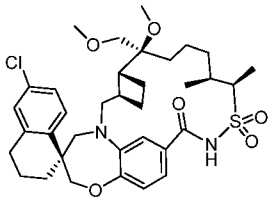
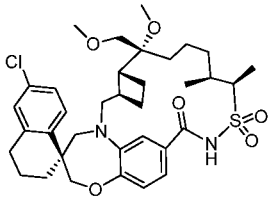
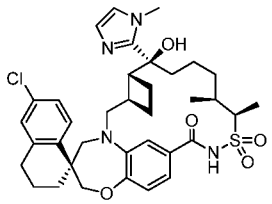
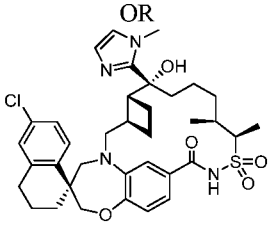
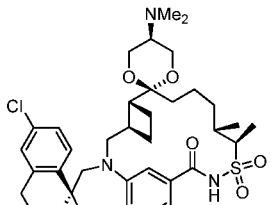
100206		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethyl-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	627.2
100207		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-ethyl-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	627.2
100208	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-propanyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-propanyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	641.2
100209	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-propyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-propyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	641.3
100210		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-propanyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.	641.2

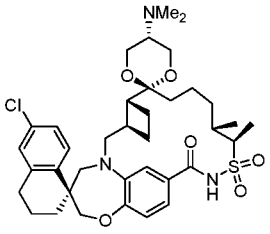
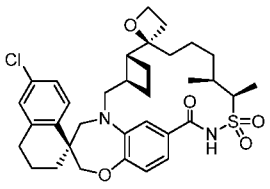
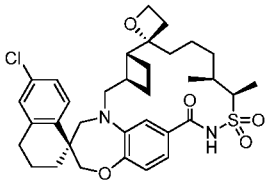
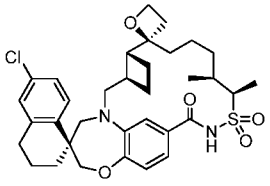
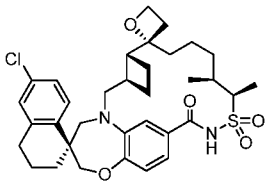
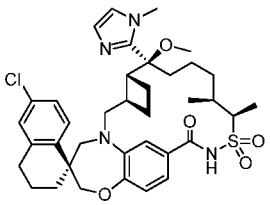
	 OR	7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-propanyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100211	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-methoxy-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-methoxy-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	629.3
100212	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-methoxy-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-methoxy-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	629.3
100213	 OR	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-cyclopropyl-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-cyclopropyl-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-	639.2

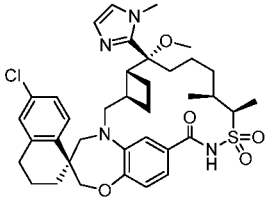
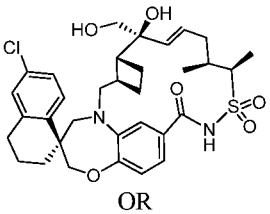
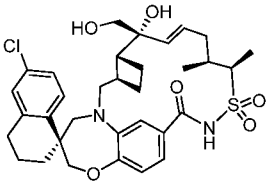
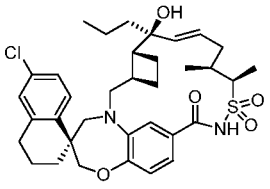
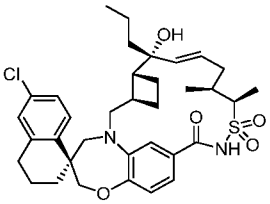
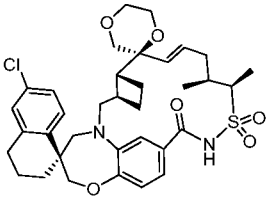
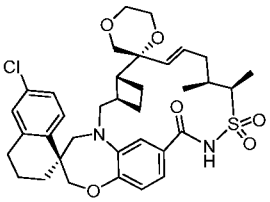
		1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100214	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-cyclopropyl-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-cyclopropyl-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	639.2
100215		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	627.2
100216	 OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-11',12'-dimethyl-3"-(4-methyl-1-piperazinyl)-3,4-dihydro-2H,4"H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',5"-[1,2]oxazol]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-11',12'-dimethyl-3"-(4-methyl-1-piperazinyl)-3,4-dihydro-2H,4"H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',5"-[1,2]oxazol]-15'-one 13',13'-dioxide	738.0

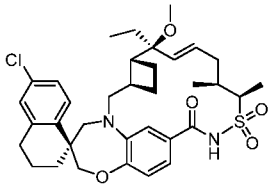
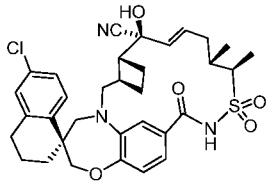
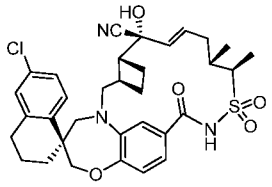
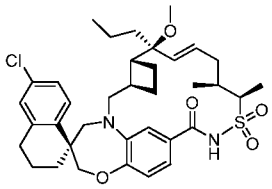
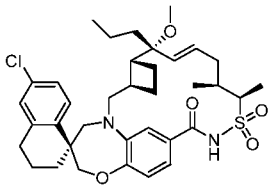
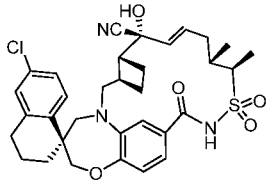
100217		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(2-hydroxyethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	657.2
100218	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-hydroxyethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(2-hydroxyethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	657.1
100219	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-hydroxyethyl)-7'-methoxy-11',12',14'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(2-hydroxyethyl)-7'-methoxy-11',12',14'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	671.1
100220	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-methylpropyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-methylpropyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.	655.2

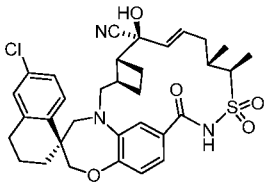
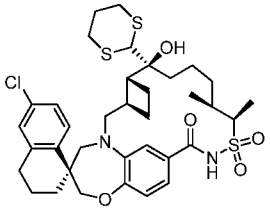
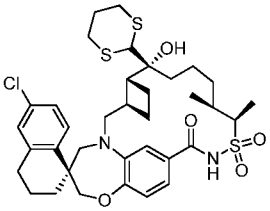
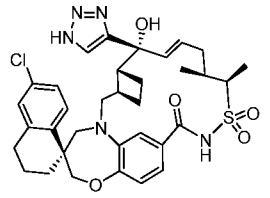
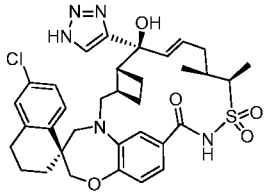
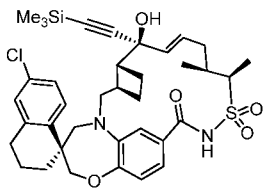
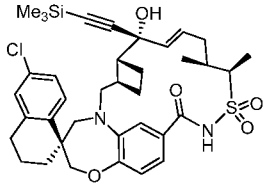
		7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100221	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(1-methyl-1H-1,2,4-triazol-5-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(1-methyl-1H-1,2,4-triazol-5-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	680.2
100222	 OR 	(1S,3'R,6'S,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(1-methyl-1H-1,2,4-triazol-5-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(1-methyl-1H-1,2,4-triazol-5-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	680.2
100223		(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(1-methyl-1H-imidazol-2-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	681.2
100224	 OR	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-methylpropyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-methylpropyl)-3,4-dihydro-2H,15'H-	655.2

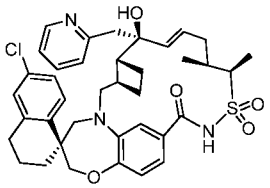
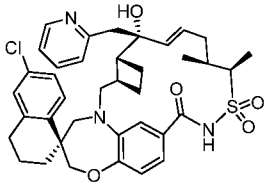
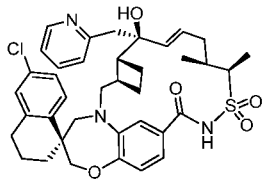
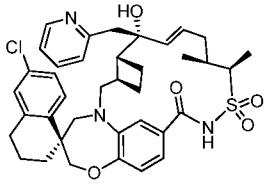
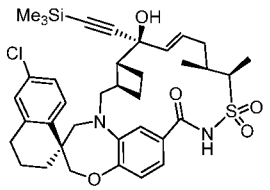
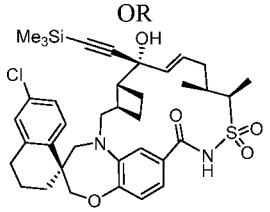
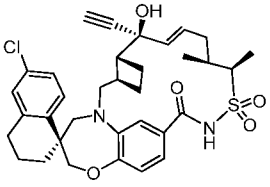
		spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100225	 OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-methoxy-7'-(methoxymethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-methoxy-7'-(methoxymethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	659.2
100226	 OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(1-methyl-1H-imidazol-2-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(1-methyl-1H-imidazol-2-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	681.2
100227	 AND	(2r,3'R,5R,6'R,11'S,12'R,22'S)-6''-chloro-5-(dimethylamino)-11',12'-dimethyl-3'',4''-dihydro-2''H,15'H-dispiro[1,3-dioxane-2,7'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-22',1''-naphthalen]-15'-one 13',13'-dioxide AND (2s,3'R,5S,6'R,11'S,12'R,22'S)-6''-chloro-5-(dimethylamino)-11',12'-dimethyl-3'',4''-dihydro-2''H,15'H-dispiro[1,3-dioxane-2,7'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24	700.1

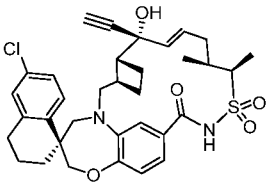
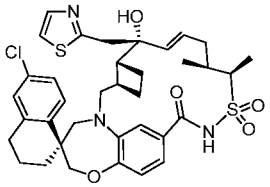
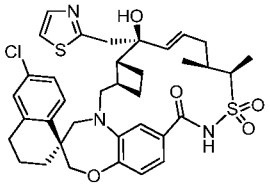
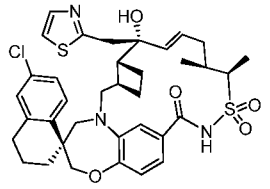
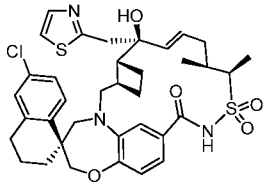
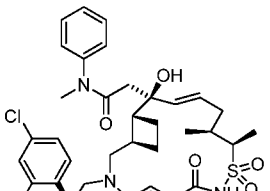
		]triene-22',1''-naphthalen]-15'-one 13',13'-dioxide	
100228	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',2''-oxetan]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',2''-oxetan]-15'-one 13',13'-dioxide	627.2
100229	 OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',2''-oxetan]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',2''-oxetan]-15'-one 13',13'-dioxide	627.2
100230	 OR	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(1-methyl-1H-imidazol-2-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(1-methyl-1H-imidazol-2-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.	695.3

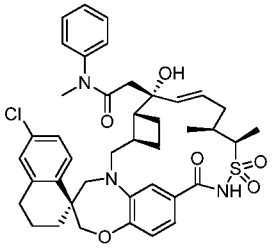
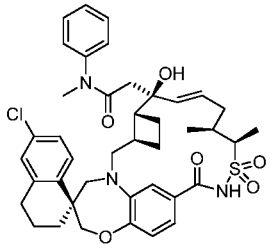
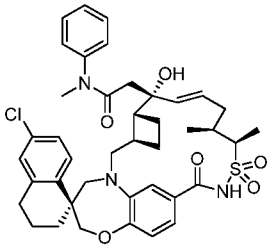
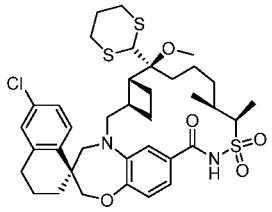
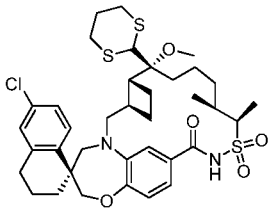
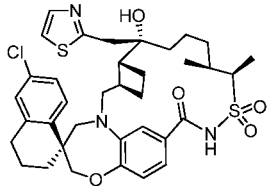
		7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	
100231	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(hydroxymethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(hydroxymethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	629.2
100232	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-propyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-propyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	641.2
100233	 OR 	(2S,3'R,6'R,8'E,11'S,12'R,22'S)-6''-chloro-11',12'-dimethyl-3'',4''-dihydro-2''H,15'H-dispiro[1,4-dioxane-2,7'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-22',1''-naphthalen]-15'-one 13',13'-dioxide OR (2R,3'R,6'R,8'E,11'S,12'R,22'S)-6''-chloro-11',12'-dimethyl-3'',4''-dihydro-2''H,15'H-dispiro[1,4-dioxane-2,7'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,	655.2

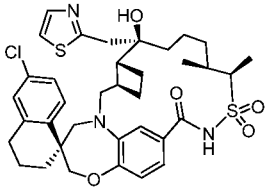
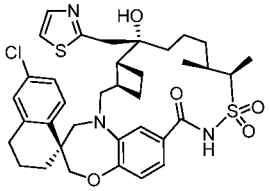
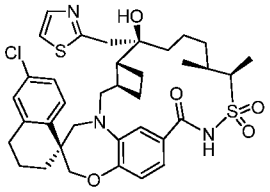
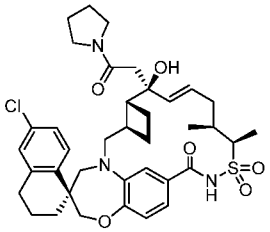
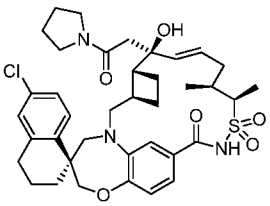
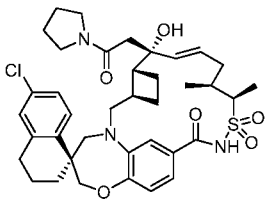
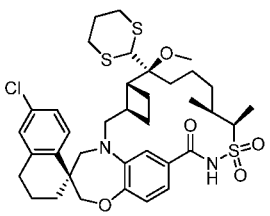
		24]tetraene-22',1''-naphthalen]-15'-one 13',13'-dioxide	
100234		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-ethyl-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	641.2
100235	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbonitrile 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbonitrile 13',13'-dioxide	624.1
100236	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-propyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-propyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	655.2
100237	 OR	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbonitrile 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-	624.1

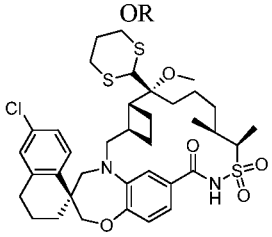
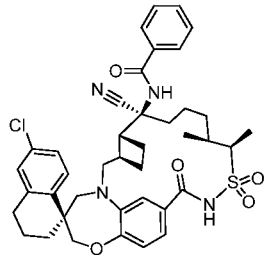
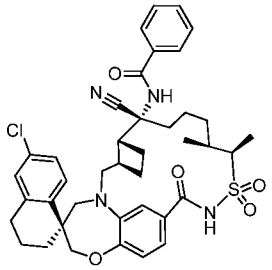
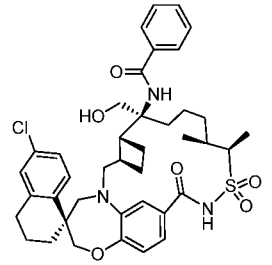
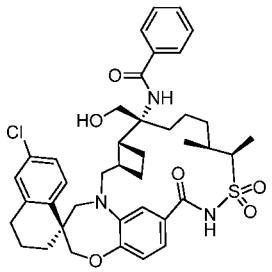
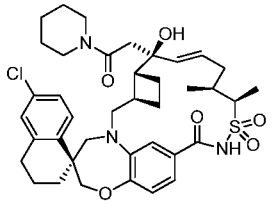
		[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbonitrile 13',13'-dioxide	
100238	 OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	719.3
100239	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(1H-1,2,3-triazol-4-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(1H-1,2,3-triazol-4-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	666.3
100240	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((trimethylsilyl)ethynyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((trimethylsilyl)ethynyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	694.4

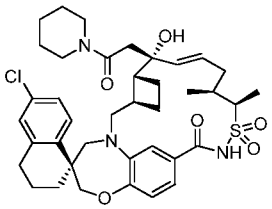
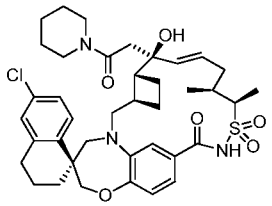
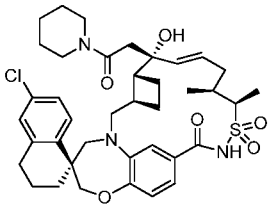
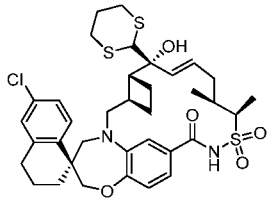
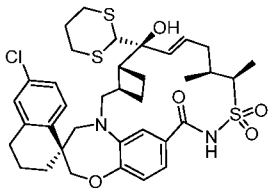
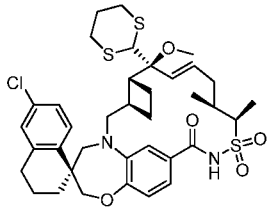
100241	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-pyridinylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-pyridinylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	690.3
100242	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-pyridinylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-pyridinylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	690.3
100243	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((trimethylsilyl)ethynyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((trimethylsilyl)ethynyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	694.4
100244		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-ethynyl-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.	623.5

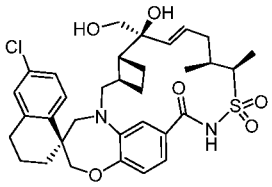
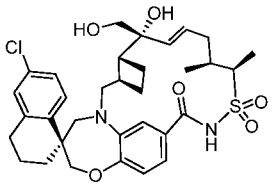
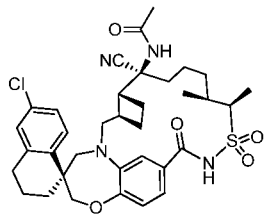
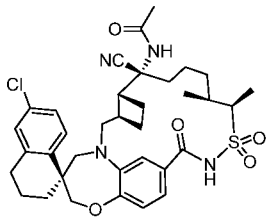
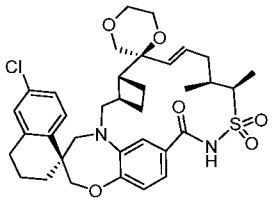
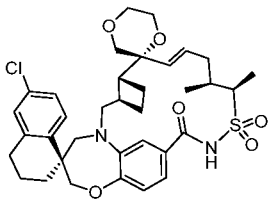
	 OR	7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethynyl-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100245	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(1,3-thiazol-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(1,3-thiazol-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	696.3
100246	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(1,3-thiazol-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(1,3-thiazol-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	696.2
100247	 OR	2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N-methyl-N-phenylacetamide OR 2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-	746.3

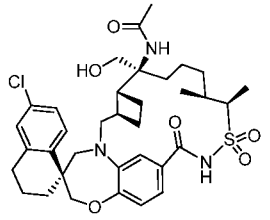
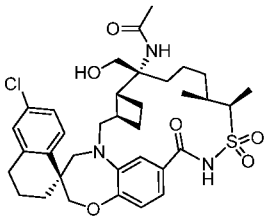
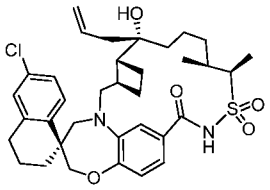
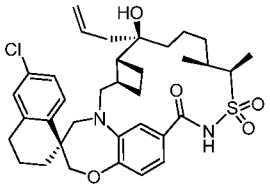
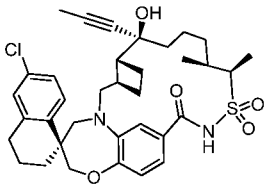
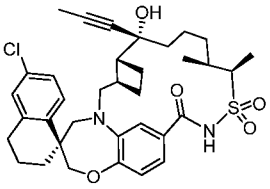
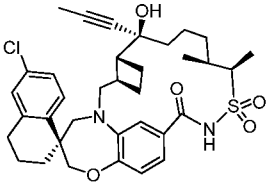
		dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N-methyl-N-phenylacetamide	
100248	 OR 	2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N-methyl-N-phenylacetamide OR 2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N-methyl-N-phenylacetamide	746.3
100249	 OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	733.4
100250	 OR	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(1,3-thiazol-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(1,3-thiazol-2-ylmethyl)-3,4-dihydro-2H,15'H-	698.3

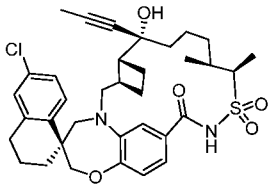
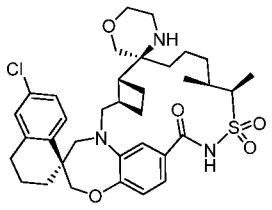
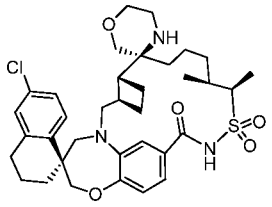
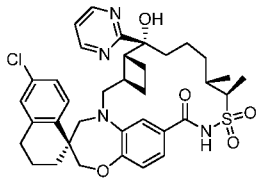
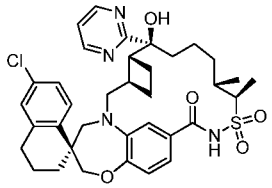
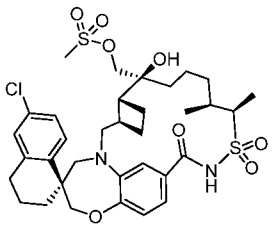
		spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	
100251	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(1,3-thiazol-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(1,3-thiazol-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	698..3
100252		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-oxo-2-(1-pyrrolidinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	710.2
100253	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-oxo-2-(1-pyrrolidinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-oxo-2-(1-pyrrolidinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	710.3
100254		(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	733.3

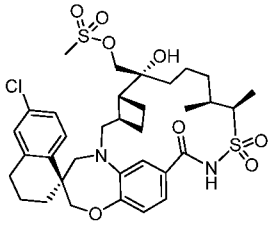
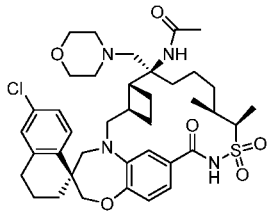
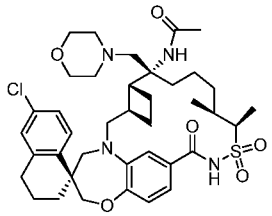
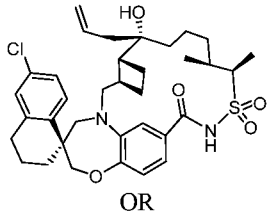
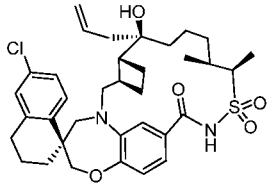
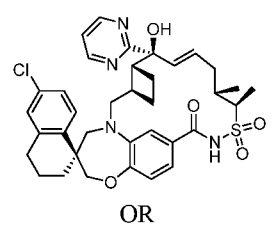
	OR 	OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	
100255	 OR 	N-((1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-cyano-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)benzamide OR N-((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-cyano-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)benzamide	729.2
100256	 OR 	N-((1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-(hydroxymethyl)-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)benzamide OR N-((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-(hydroxymethyl)-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)benzamide	734.2
100257		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-oxo-2-(1-piperidinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.	724.2

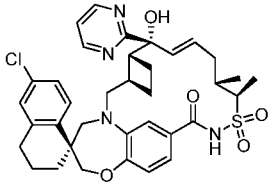
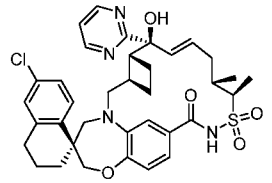
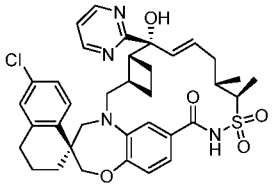
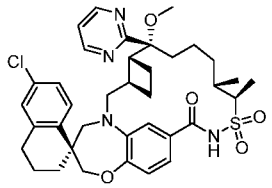
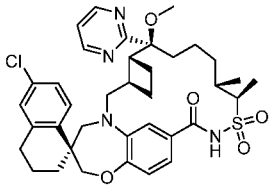
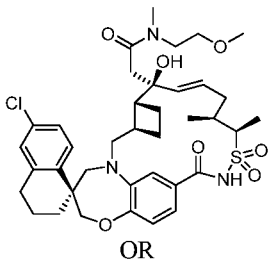
	OR 	7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-oxo-2-(1-piperidinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100258	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-oxo-2-(1-piperidinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-oxo-2-(1-piperidinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	724.2
100259		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	717.0
100260		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	717.2
100261		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	731.5

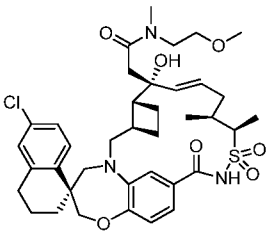
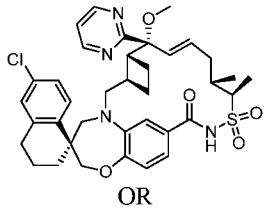
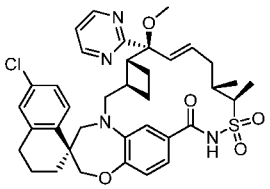
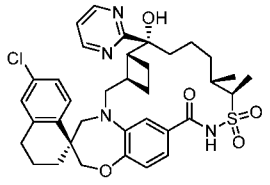
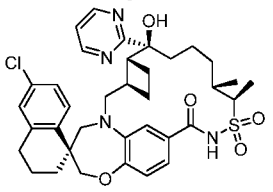
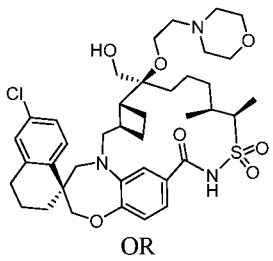
100262	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(hydroxymethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(hydroxymethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	629.2
100263	 OR 	N-((1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-cyano-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)acetamide OR N-((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-cyano-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)acetamide	667.2
100264	 OR 	(2S,3'R,6'R,8'E,11'S,12'R,22'S)-6''-chloro-11',12'-dimethyl-3'',4''-dihydro-2''H,15'H-dispiro[1,4-dioxane-2,7'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-22',1''-naphthalen]-15'-one 13',13'-dioxide OR (2R,3'R,6'R,8'E,11'S,12'R,22'S)-6''-chloro-11',12'-dimethyl-3'',4''-dihydro-2''H,15'H-dispiro[1,4-dioxane-2,7'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene-22',1''-naphthalen]-15'-one 13',13'-dioxide	655.2

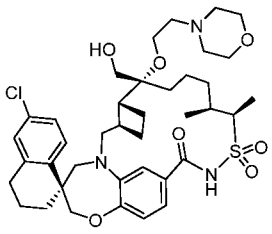
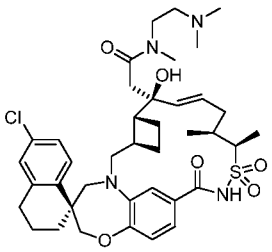
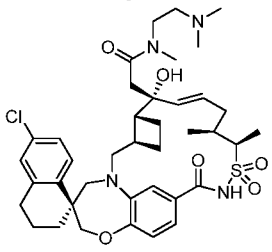
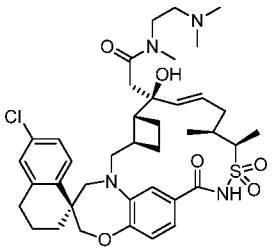
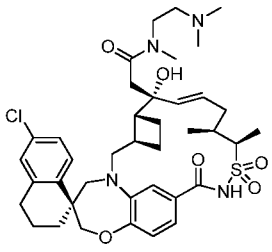
100265	 OR 	N-((1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-(hydroxymethyl)-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)acetamide OR N-((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-(hydroxymethyl)-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)acetamide	672.2
100266	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-propen-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-propen-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	641.2
100267	 OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(1-propyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(1-propyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	639.2
100268		(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(1-propyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.	639.3

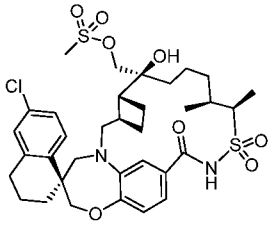
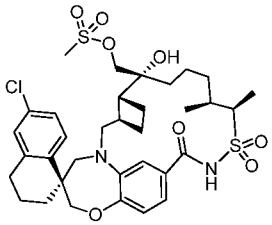
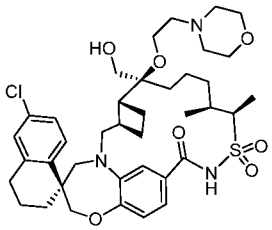
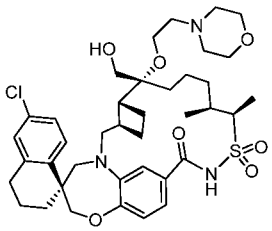
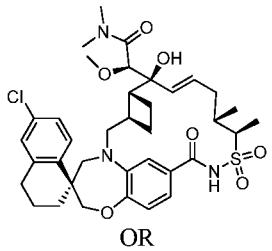
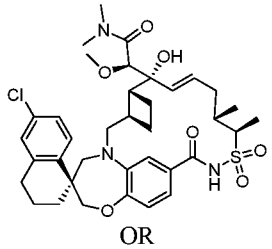
	OR 	7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(1-propyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	
100269	 OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',3''-[1,4]oxazinan]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,15'H-dispiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-7',3''-[1,4]oxazinan]-15'-one 13',13'-dioxide	656.2
100270	 AND 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-pyrimidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-pyrimidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	679.2
100271	 OR	((1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)methyl methanesulfonate OR ((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-	709.1

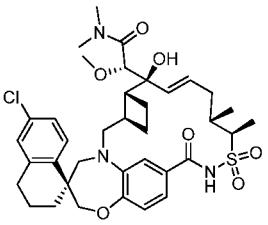
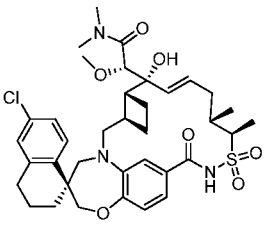
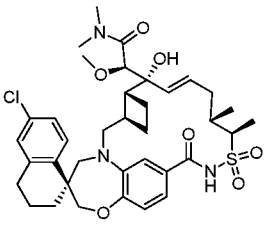
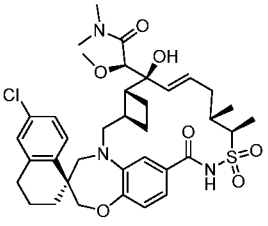
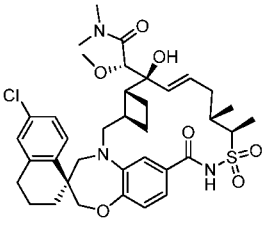
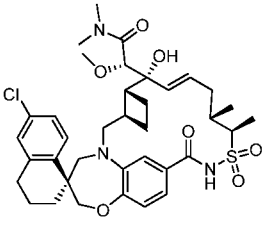
		spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)methyl methanesulfonate	
100272	 OR 	N-((1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-11',12'-dimethyl-7'-(4-morpholinylmethyl)-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)acetamide OR N-((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-11',12'-dimethyl-7'-(4-morpholinylmethyl)-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)acetamide	741.2
100273	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-propen-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-propen-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	641.3
100274	 OR	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-pyrimidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-	677.3

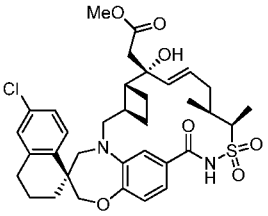
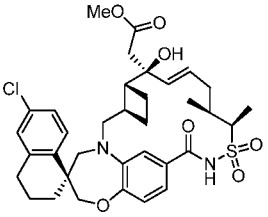
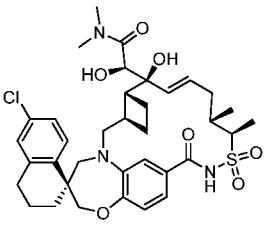
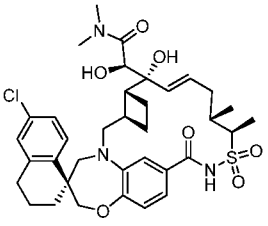
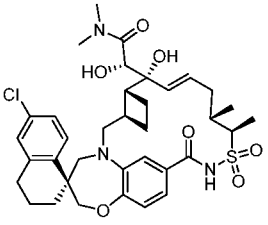
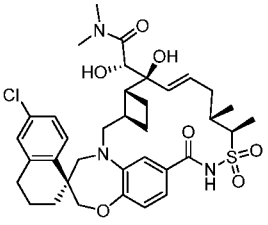
		pyrimidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100275	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-pyrimidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-pyrimidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	677.3
100276	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-pyrimidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-pyrimidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	693.3
100277	 OR	2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N-(2-methoxyethyl)-N-methylacetamide OR 2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,	728.2

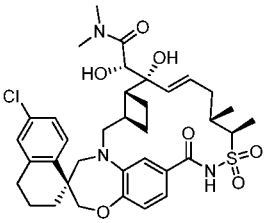
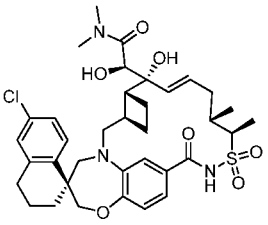
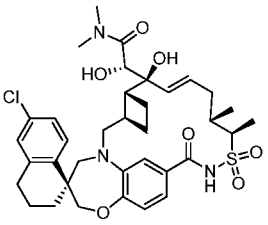
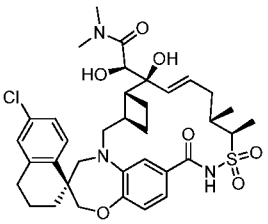
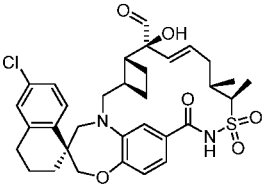
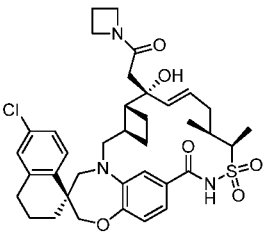
		24]tetraen]-7'-yl)-N-(2-methoxyethyl)-N-methylacetamide	
100278	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-pyrimidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-pyrimidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	691.2
100279	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-pyrimidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-pyrimidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	679.2
100280	 OR	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-(hydroxymethyl)-11',12'-dimethyl-7'-(2-(4-morpholinyl)ethoxy)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-(hydroxymethyl)-11',12'-dimethyl-7'-(2-(4-morpholinyl)ethoxy)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.	744.3

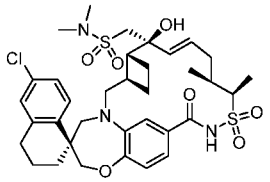
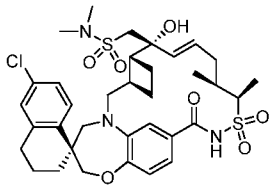
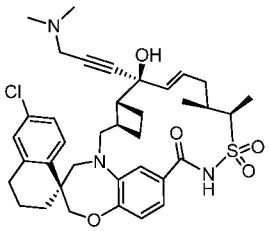
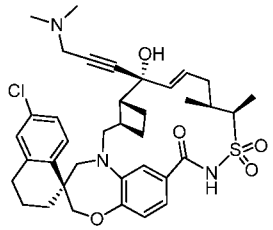
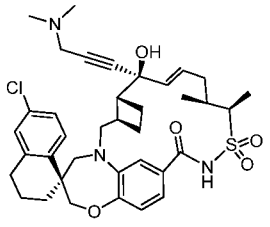
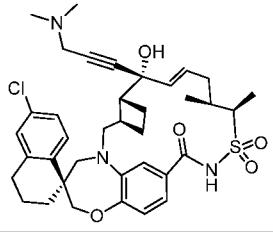
		7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	
100281	 OR 	2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N-(2-(dimethylamino)ethyl)-N-methylacetamide OR 2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N-(2-(dimethylamino)ethyl)-N-methylacetamide	741.2
100282	 OR 	2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N-(2-(dimethylamino)ethyl)-N-methylacetamide OR 2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N-(2-(dimethylamino)ethyl)-N-methylacetamide	741.3

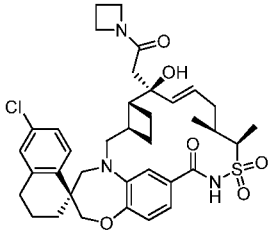
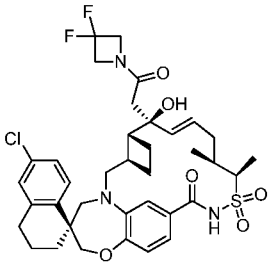
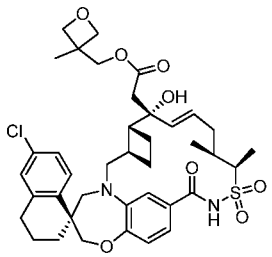
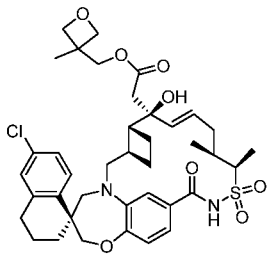
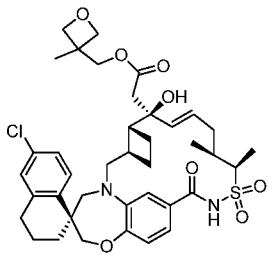
100283	 OR 	((1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)methyl methanesulfonate OR ((1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-7'-yl)methyl methanesulfonate	709.1
100284	 OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-(hydroxymethyl)-11',12'-dimethyl-7'-(2-(4-morpholinyl)ethoxy)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-(hydroxymethyl)-11',12'-dimethyl-7'-(2-(4-morpholinyl)ethoxy)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	744.3
100285	 OR  OR	(2R)-2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-2-methoxy-N,N-dimethylethanamide OR (2R)-2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-2-methoxy-N,N-dimethylethanamide OR (2S)-2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-	714.2

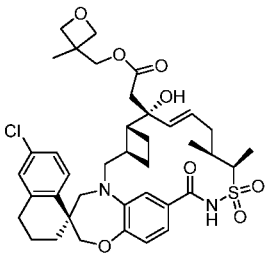
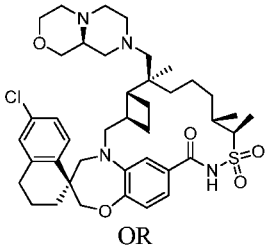
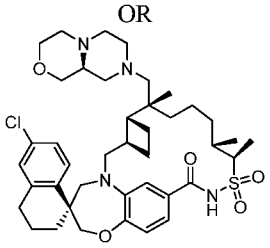
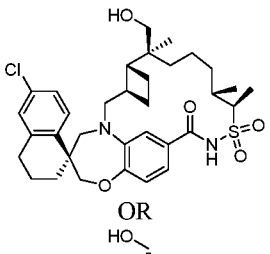
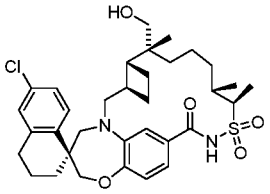
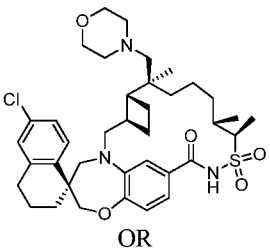
	 OR 	13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-2-methoxy-N,N-dimethylethanamide OR (2S)-2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-2-methoxy-N,N-dimethylethanamide	
100286	 OR  OR  OR 	(2R)-2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-2-methoxy-N,N-dimethylethanamide OR (2R)-2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-2-methoxy-N,N-dimethylethanamide OR (2S)-2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-2-methoxy-N,N-dimethylethanamide OR (2S)-2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-2-methoxy-N,N-dimethylethanamide	714.2

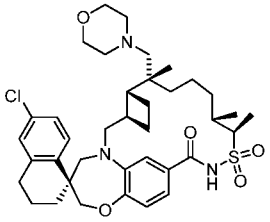
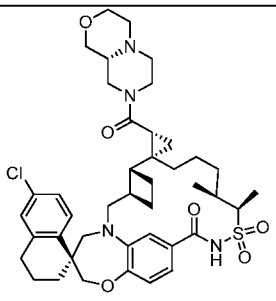
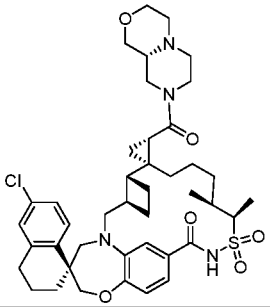
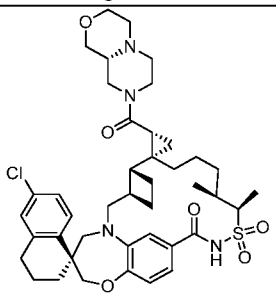
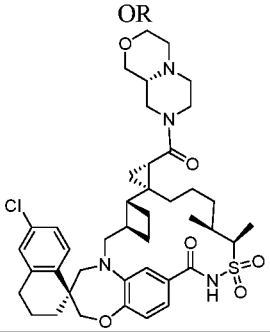
100287		methyl ((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetate	671.2
100288		methyl ((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetate	671.2
100289	 OR  OR  OR 	(2R)-2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-2-hydroxy-N,N-dimethylethanamide OR (2S)-2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-2-hydroxy-N,N-dimethylethanamide OR (2S)-2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-2-hydroxy-N,N-dimethylacetamide OR (2S)-2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-2-hydroxy-N,N-dimethylethanamide	700.3

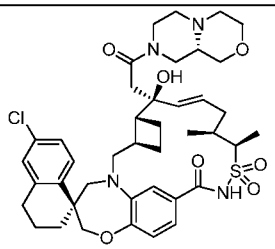
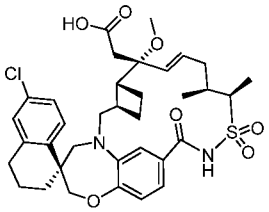
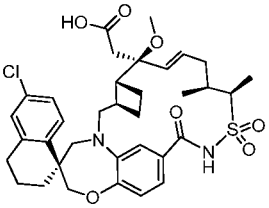
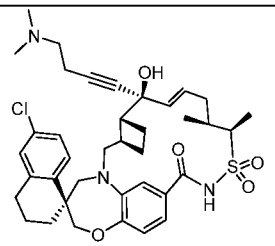
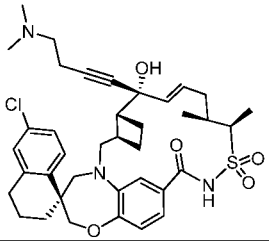
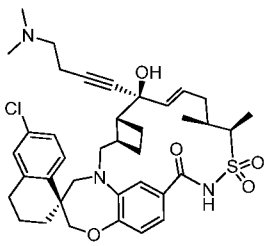
100290	 OR  OR  OR 	(2S)-2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-2-hydroxy-N,N-dimethylethanamide OR (2R)-2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-2-hydroxy-N,N-dimethylethanamide OR (2S)-2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-2-hydroxy-N,N-dimethylethanamide OR (2R)-2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-2-hydroxy-N,N-dimethylethanamide	700.3
100291		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide	627.3
100292		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-7'-(2-(1-azetidinyl)-2-oxoethyl)-6-chloro-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	696.2

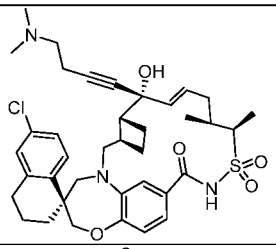
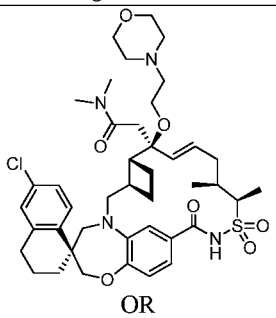
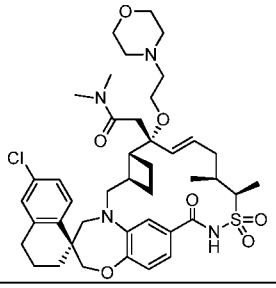
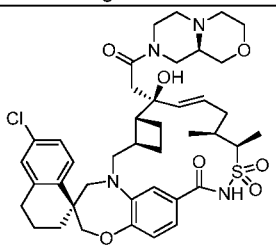
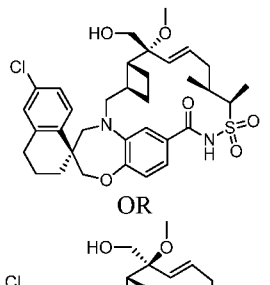
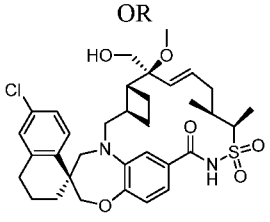
100293	 OR 	1-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-dimethylmethanesulfonamide OR 1-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-dimethylmethanesulfonamide	720.2
100294	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(3-(dimethylamino)-1-propyn-1-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(3-(dimethylamino)-1-propyn-1-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	680.3
100295	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(3-(dimethylamino)-1-propyn-1-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(3-(dimethylamino)-1-propyn-1-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	680.5

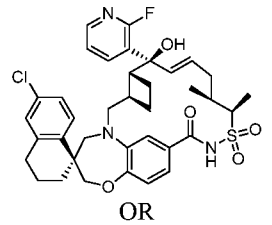
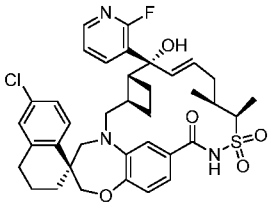
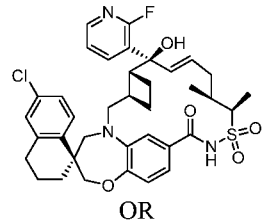
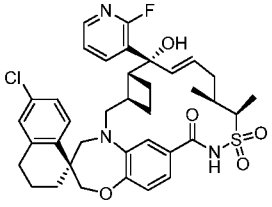
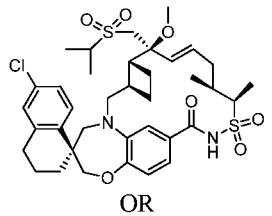
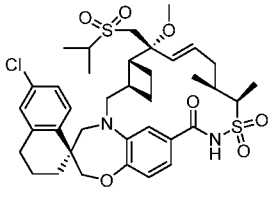
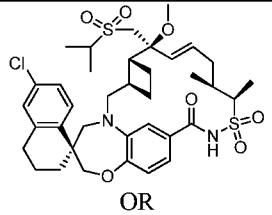
100296		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-7'-(2-(1-azetidinyl)-2-oxoethyl)-6-chloro-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	696.2
100297		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-(3,3-difluoro-1-azetidinyl)-2-oxoethyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	732.2
100298	 OR 	(3-methyl-3-oxetanyl)methyl ((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetate OR (3-methyl-3-oxetanyl)methyl ((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetate	741.2
100299	 OR	(3-methyl-3-oxetanyl)methyl ((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetate OR (3-methyl-3-oxetanyl)methyl ((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.	741.2

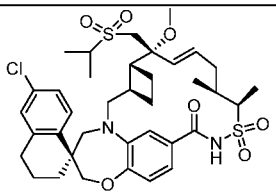
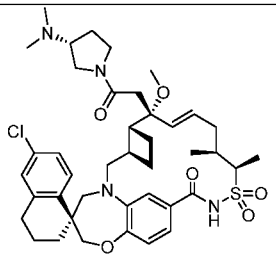
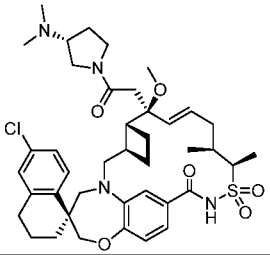
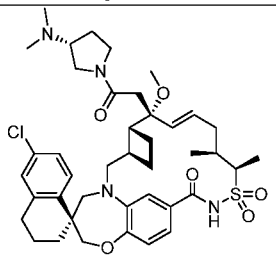
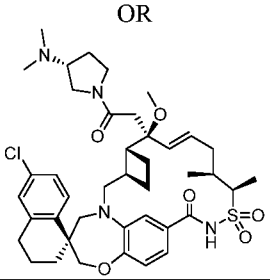
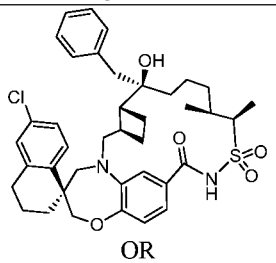
		7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetate	
100300	 OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl)-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	753.3
100301	 OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-(hydroxymethyl)-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-(hydroxymethyl)-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	629.4
100302	 OR	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7',11',12'-trimethyl-7'-(4-morpholinylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7',11',12'-trimethyl-7'-(4-morpholinylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-	698.5

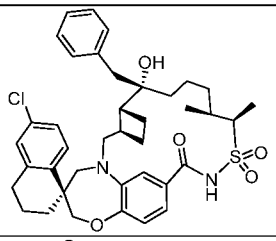
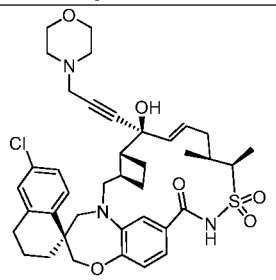
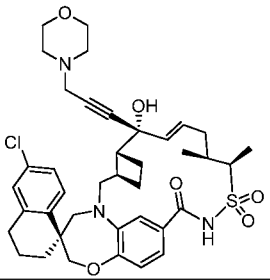
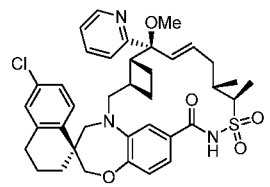
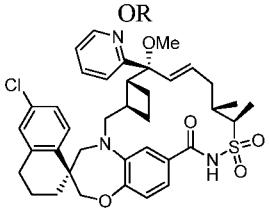
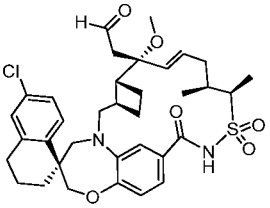
		[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	
100303	 OR 	(1R,2R,3'R,6'R,11'S,12'R,22'S)-6''-chloro-2-((9aR)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylcarbonyl)-11',12'-dimethyl-3'',4''-dihydro-2''H,15'H-dispiro[cyclopropane-1,7'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-22',1''-naphthalen]-15'-one 13',13'-dioxide OR (1R,2S,3'R,6'R,11'S,12'R,22'S)-6''-chloro-2-((9aR)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylcarbonyl)-11',12'-dimethyl-3'',4''-dihydro-2''H,15'H-dispiro[cyclopropane-1,7'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-22',1''-naphthalen]-15'-one 13',13'-dioxide	779.3
100304	 OR 	(1R,2R,3'R,6'R,11'S,12'R,22'S)-6''-chloro-2-((9aR)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylcarbonyl)-11',12'-dimethyl-3'',4''-dihydro-2''H,15'H-dispiro[cyclopropane-1,7'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-22',1''-naphthalen]-15'-one 13',13'-dioxide OR (1R,2S,3'R,6'R,11'S,12'R,22'S)-6''-chloro-2-((9aR)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylcarbonyl)-11',12'-dimethyl-3'',4''-dihydro-2''H,15'H-dispiro[cyclopropane-1,7'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-22',1''-naphthalen]-15'-one 13',13'-dioxide	779.3

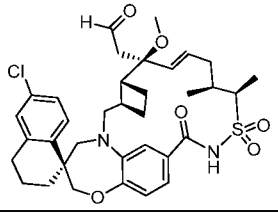
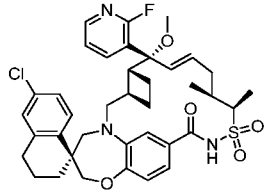
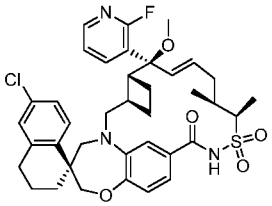
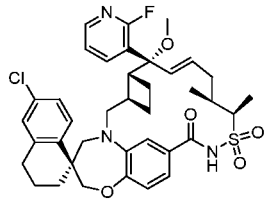
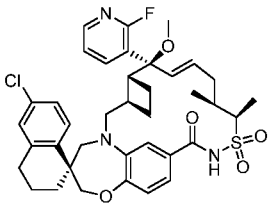
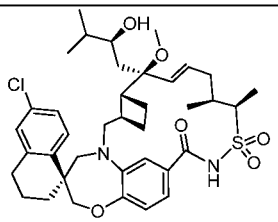
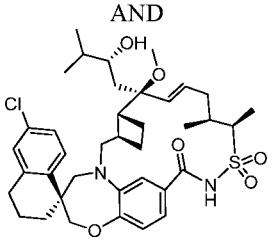
100305		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-2-oxoethyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	781.2
100306		((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetic acid	671.2
100307		((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetic acid	671.2
100308	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(4-(dimethylamino)-1-butyn-1-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(4-(dimethylamino)-1-butyn-1-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	694.5
100309	 OR	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(4-(dimethylamino)-1-butyn-1-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(4-(dimethylamino)-1-butyn-1-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.	694.5

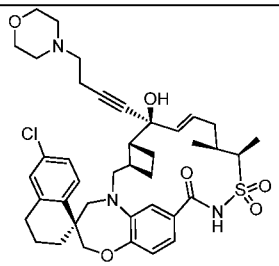
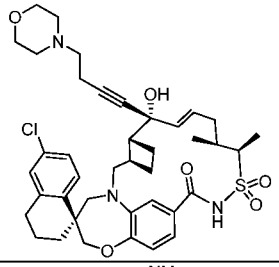
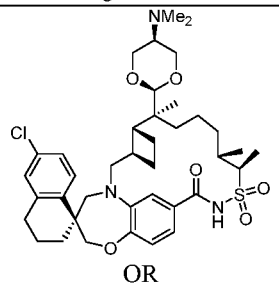
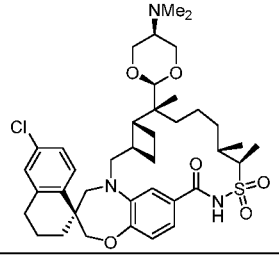
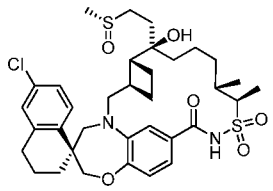
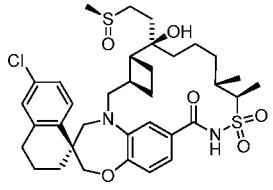
		7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100310	 OR 	2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-7'-(2-(4-morpholinyl)ethoxy)-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-dimethylacetamide OR 2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-7'-(2-(4-morpholinyl)ethoxy)-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-dimethylacetamide	797.3
100311		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-((9aR)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-2-oxoethyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	781.2
100312	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(hydroxymethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(hydroxymethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	643.2

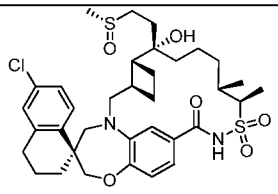
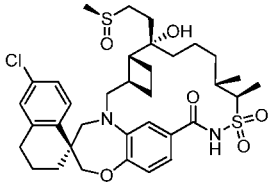
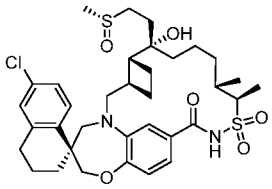
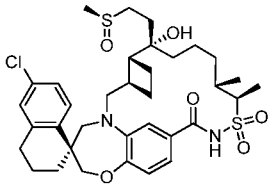
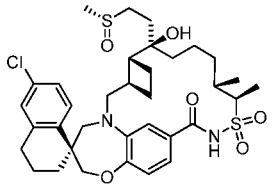
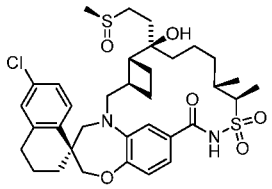
100313	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(2-fluoro-3-pyridinyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-fluoro-3-pyridinyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	694.3
100314	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(2-fluoro-3-pyridinyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-fluoro-3-pyridinyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	694.3
100315	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((2-propanylsulfonyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((2-propanylsulfonyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	733.3
100316	 OR	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((2-propanylsulfonyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	733.3

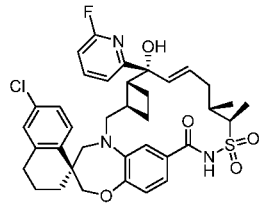
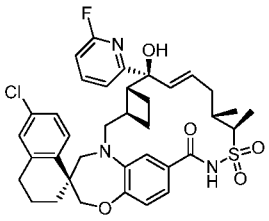
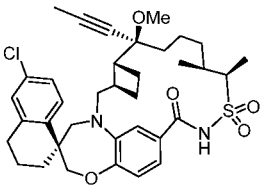
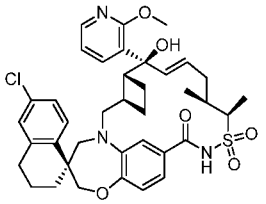
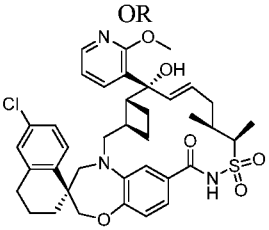
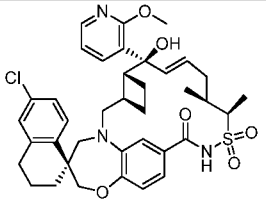
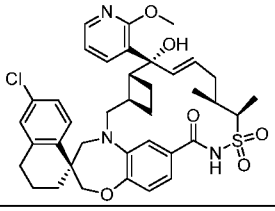
		OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((2-propanylsulfonyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100317	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(2-((3R)-3-(dimethylamino)-1-pyrrolidinyl)-2-oxoethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-((3R)-3-(dimethylamino)-1-pyrrolidinyl)-2-oxoethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	767.3
100318	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-((3R)-3-(dimethylamino)-1-pyrrolidinyl)-2-oxoethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(2-((3R)-3-(dimethylamino)-1-pyrrolidinyl)-2-oxoethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	767.3
100319	 OR	(1S,3'R,6'R,7'S,11'S,12'R)-7'-benzyl-6-chloro-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR	691.2

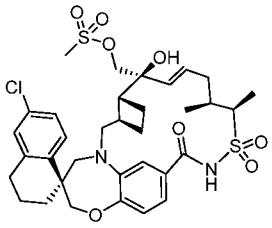
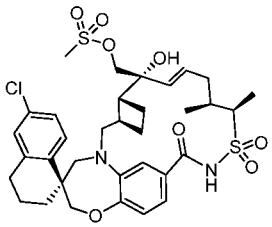
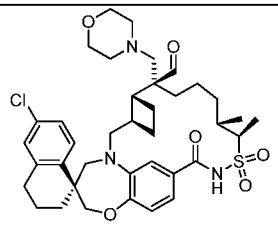
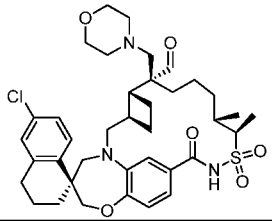
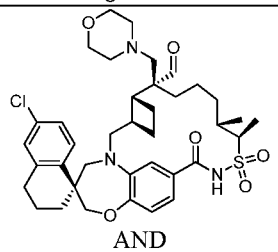
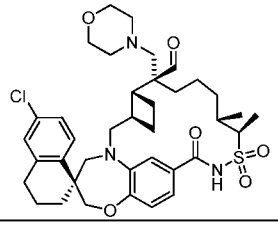
		(1S,3'R,6'R,7'R,11'S,12'R)-7'-benzyl-6-chloro-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	
100320	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(3-(4-morpholinyl)-1-propyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(3-(4-morpholinyl)-1-propyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	722.2
100321	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	690.0
100322		((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetaldehyde	655.2

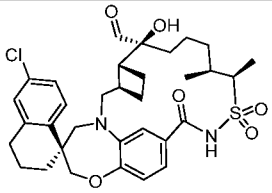
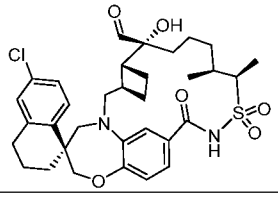
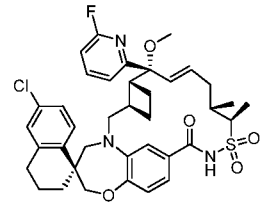
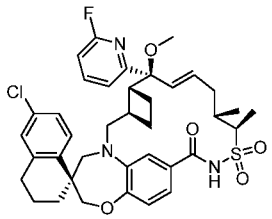
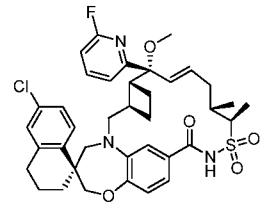
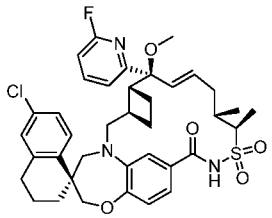
100323		((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetaldehyde	655.2
100324	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(2-fluoro-3-pyridinyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-fluoro-3-pyridinyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	707.2
100325	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(2-fluoro-3-pyridinyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-fluoro-3-pyridinyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	707.3
100326	 AND 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((2R)-2-hydroxy-3-methylbutyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND |(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((2S)-2-hydroxy-3-methylbutyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	699.2

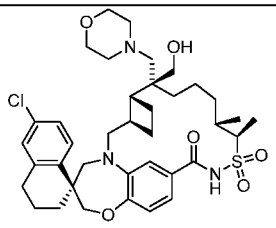
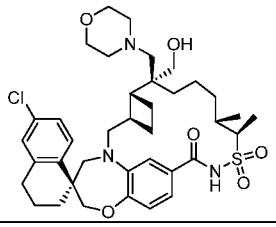
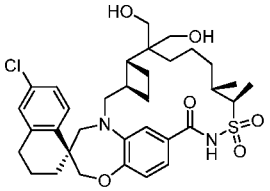
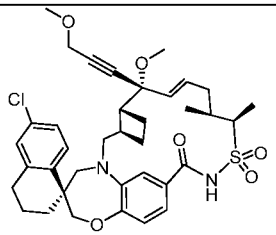
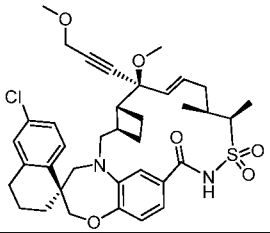
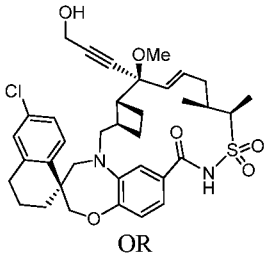
100327	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(4-(4-morpholinyl)-1-butyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(4-(4-morpholinyl)-1-butyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	736.4
100328	 OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-(cis-5-(dimethylamino)-1,3-dioxan-2-yl)-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-(cis-5-(dimethylamino)-1,3-dioxan-2-yl)-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	728.3
100329	 AND  OR	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-((R)-methylsulfinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-((S)-methylsulfinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR	691.3

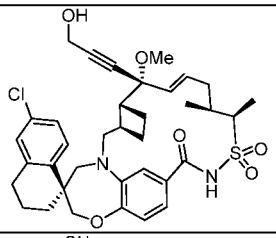
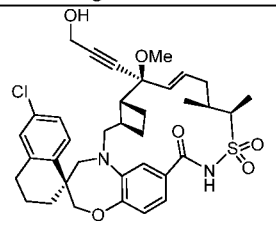
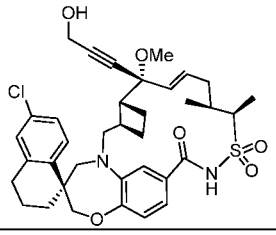
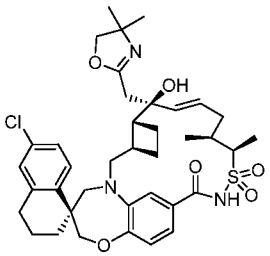
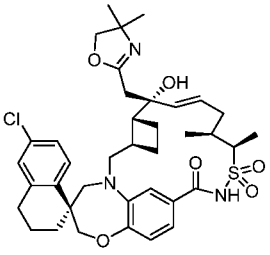
	 AND 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-((R)-methylsulfinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-((S)-methylsulfinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	
100330	 AND  OR  AND 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-((R)-methylsulfinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-((S)-methylsulfinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-((R)-methylsulfinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-((S)-methylsulfinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	691.3

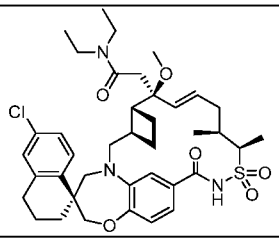
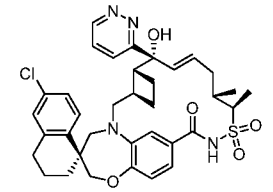
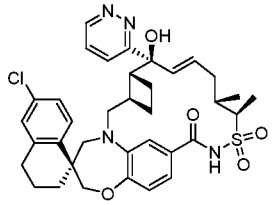
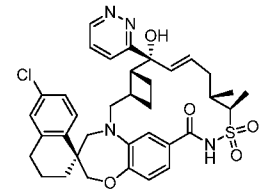
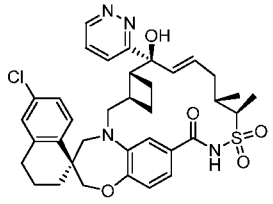
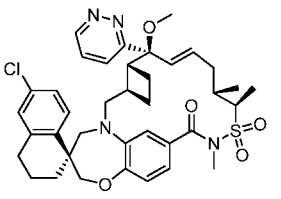
100331	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(6-fluoro-2-pyridinyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(6-fluoro-2-pyridinyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	694.0
100332		(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(1-propyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	653.3
100333	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(2-methoxy-3-pyridinyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(2-methoxy-3-pyridinyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	706.3
100334	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(2-methoxy-3-pyridinyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(2-methoxy-3-pyridinyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.	706.3

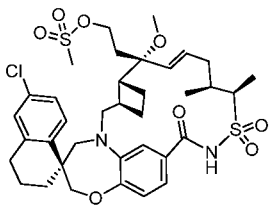
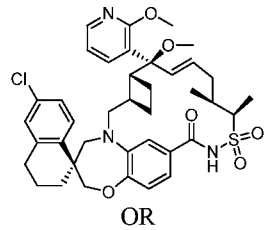
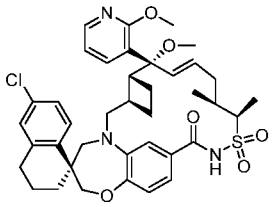
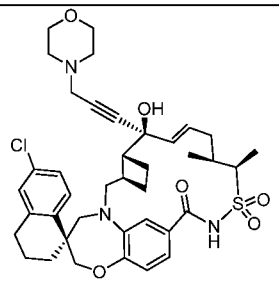
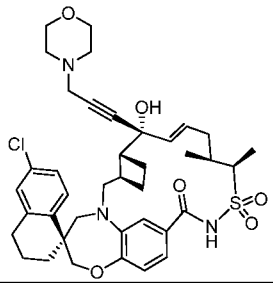
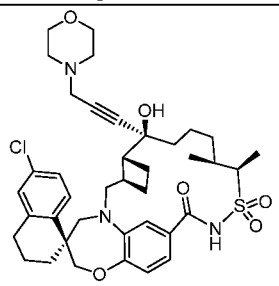
		7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100335	 OR 	((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)methyl methanesulfonate OR ((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)methyl methanesulfonate	707.2
100336	 OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-11',12'-dimethyl-7'-(4-morpholinylmethyl)-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene]-7'-carbaldehyde 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-11',12'-dimethyl-7'-(4-morpholinylmethyl)-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene]-7'-carbaldehyde 13',13'-dioxide	712.5
100337	 AND 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-11',12'-dimethyl-7'-(4-morpholinylmethyl)-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene]-7'-carbaldehyde 13',13'-dioxide AND (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-11',12'-dimethyl-7'-(4-morpholinylmethyl)-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene]-7'-carbaldehyde 13',13'-dioxide	712.5

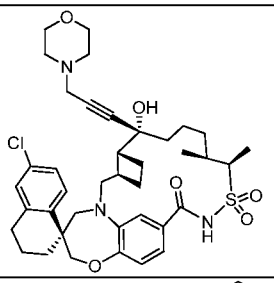
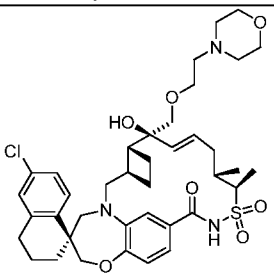
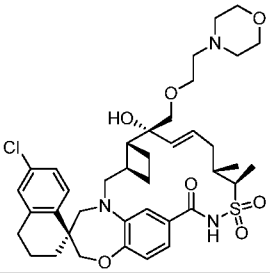
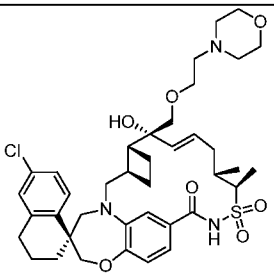
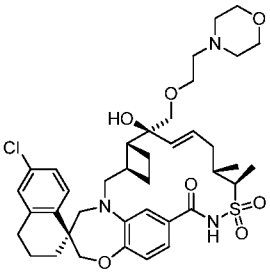
100338	 OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene]-7'-carbaldehyde 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene]-7'-carbaldehyde 13',13'-dioxide	629.2
100339	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(6-fluoro-2-pyridinyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(6-fluoro-2-pyridinyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	676.0
100340	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(6-fluoro-2-pyridinyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(6-fluoro-2-pyridinyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	676.0

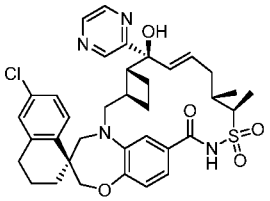
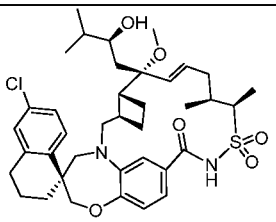
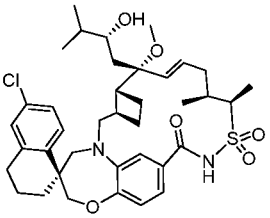
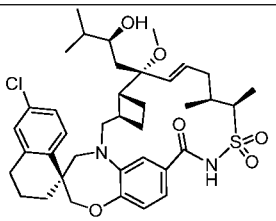
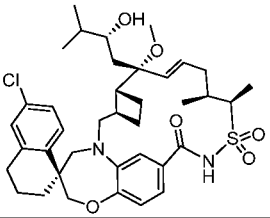
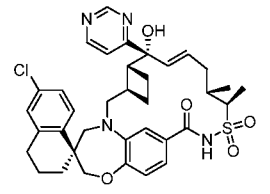
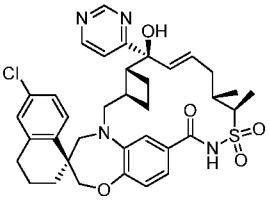
100341	 OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-(hydroxymethyl)-11',12'-dimethyl-7'-(4-morpholinylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-(hydroxymethyl)-11',12'-dimethyl-7'-(4-morpholinylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	714.3
100342		(1S,3'R,6'R,11'S,12'R)-6-chloro-7',7'-bis(hydroxymethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	645.2
100343	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-7'-(3-methoxy-1-propyn-1-yl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-7'-(3-methoxy-1-propyn-1-yl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	681.5
100344	 OR	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(3-hydroxy-1-propyn-1-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(3-hydroxy-1-propyn-1-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.	667.2

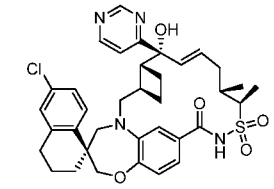
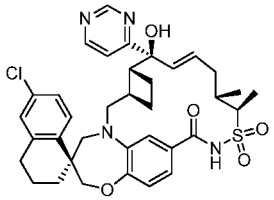
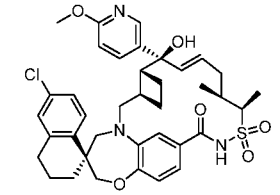
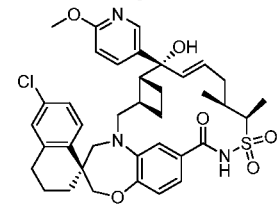
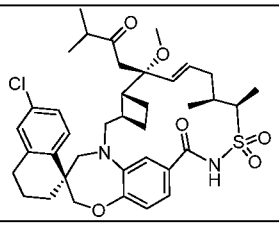
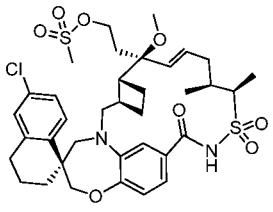
		7.2.0~3,6~.0~19,24~]pentacosa[8,16,18, 24]tetraen]-15'-one 13',13'-dioxide	
100345	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(3-hydroxy-1-propyn-1-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18, 24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(3-hydroxy-1-propyn-1-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18, 24]tetraen]-15'-one 13',13'-dioxide	667.2
100346	 AND 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)methyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18, 24]tetraen]-15'-one 13',13'-dioxide|(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)methyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18, 24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)methyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18, 24]tetraen]-15'-one 13',13'-dioxide|(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)methyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-	710.0

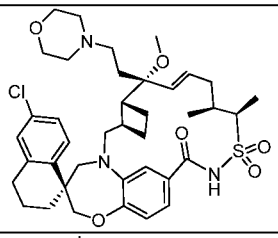
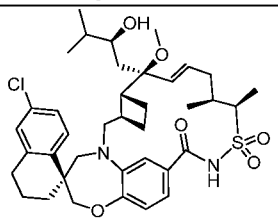
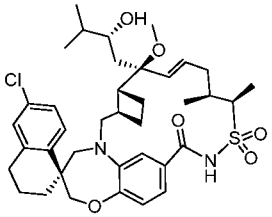
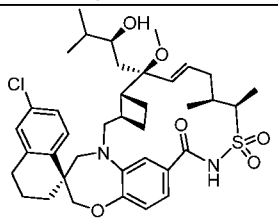
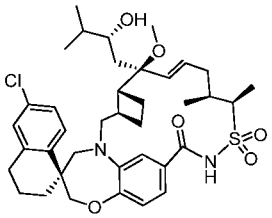
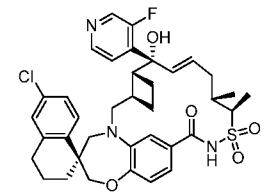
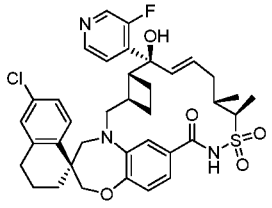
		spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100347		2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N,N-diethylacetamide	748.2
100348	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(3-pyridazinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(3-pyridazinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	677.0
100349	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(3-pyridazinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(3-pyridazinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	677.0
100350		3-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-1-methylpyridazin-1-ium	705.0

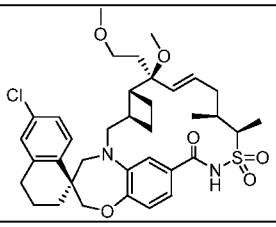
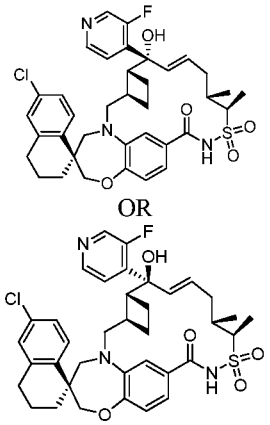
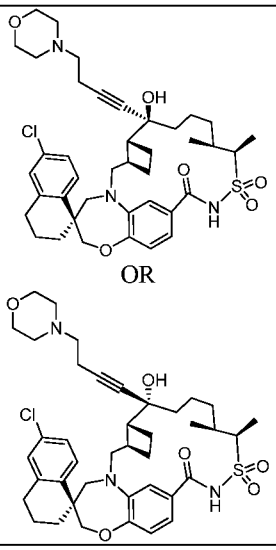
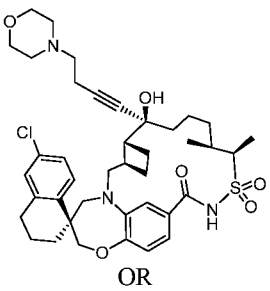
100351		2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)ethyl methanesulfonate	757.1 (M+Na)
100352	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-7'-(2-methoxy-3-pyridinyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-7'-(2-methoxy-3-pyridinyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	720.2
100353	 OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(3-(4-morpholinyl)-1-propyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(3-(4-morpholinyl)-1-propyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	724.3
100354	 OR	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(3-(4-morpholinyl)-1-propyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(3-(4-	724.3

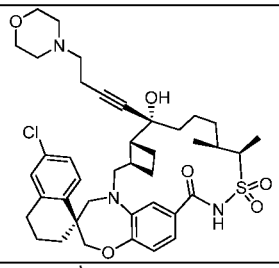
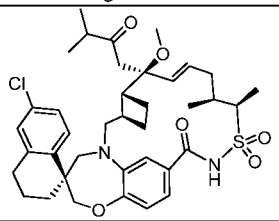
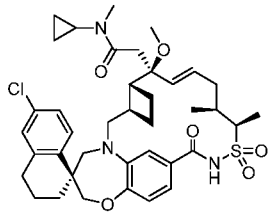
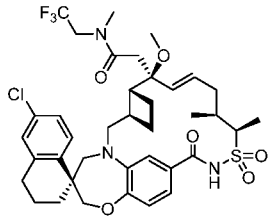
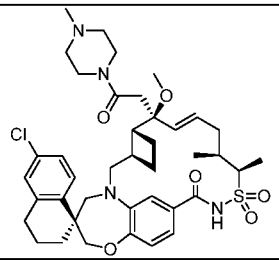
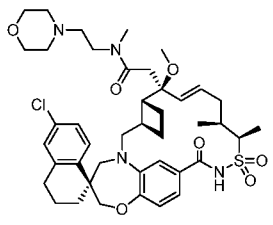
		morpholinyl)-1-propyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	
100355	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((2-(4-morpholinyl)ethoxy)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((2-(4-morpholinyl)ethoxy)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	742.3
100356	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((2-(4-morpholinyl)ethoxy)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'S,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((2-(4-morpholinyl)ethoxy)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	742.3

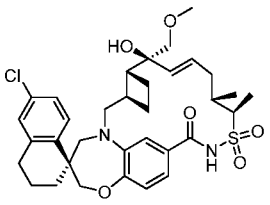
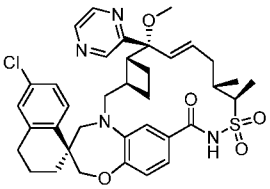
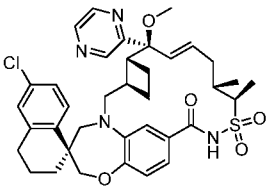
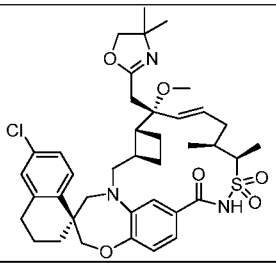
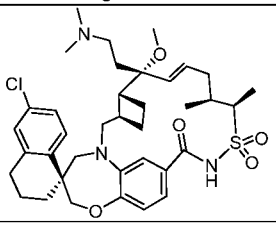
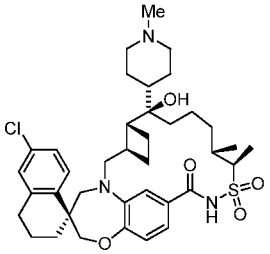
100357		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-pyrazinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	677.0
100358	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((2S)-2-hydroxy-3-methylbutyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((2R)-2-hydroxy-3-methylbutyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	721.5 (M+Na)
100359	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((2S)-2-hydroxy-3-methylbutyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((2R)-2-hydroxy-3-methylbutyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	721.5 (M+Na)
100360	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(4-pyrimidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(4-pyrimidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	677.0

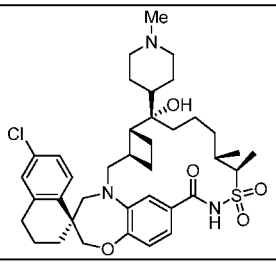
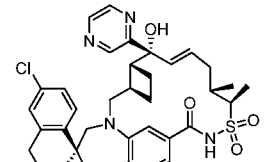
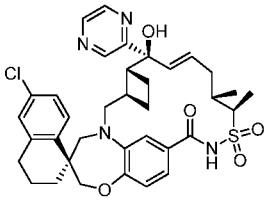
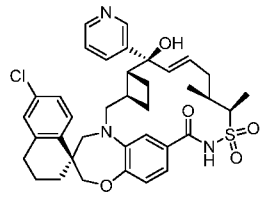
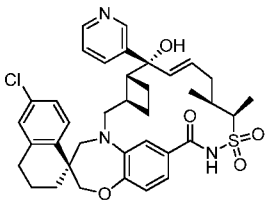
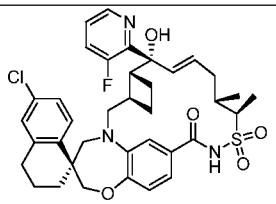
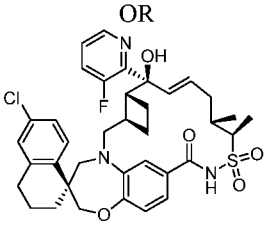
100361	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(4-pyrimidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(4-pyrimidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	677.0
100362	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(6-methoxy-3-pyridinyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(6-methoxy-3-pyridinyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	706.3
100363		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(3-methyl-2-oxobutyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	697.2
100364		2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)ethyl methanesulfonate	757.2 (M+Na)

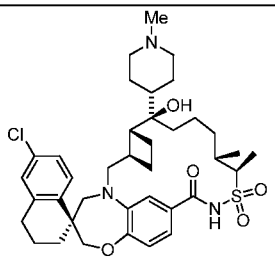
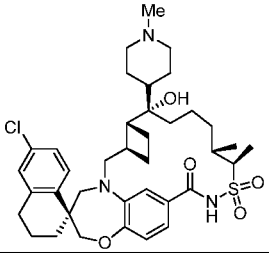
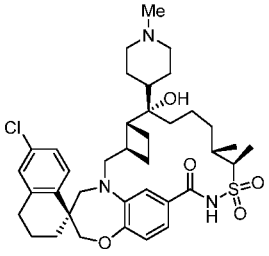
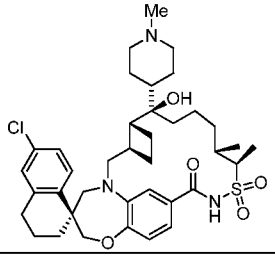
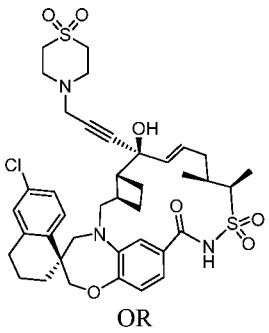
100365		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-(4-morpholinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	726.3
100366	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((2R)-2-hydroxy-3-methylbutyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR |(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((2S)-2-hydroxy-3-methylbutyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	721.3 (M+Na)
100367	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((2R)-2-hydroxy-3-methylbutyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR |(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((2S)-2-hydroxy-3-methylbutyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	721.3 (M+Na)
100368	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(3-fluoro-4-pyridinyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(3-fluoro-4-pyridinyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	694.0

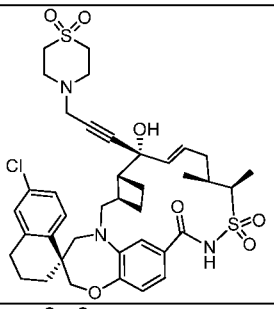
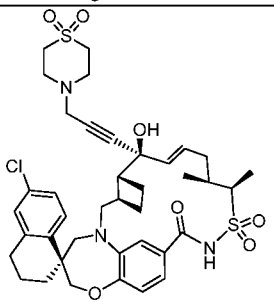
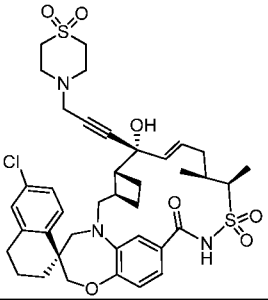
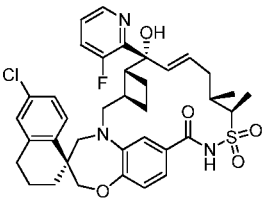
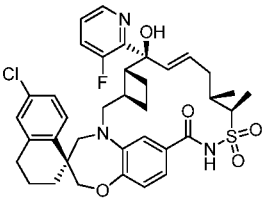
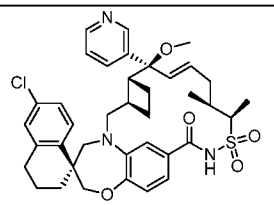
100369		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-7'-(2-methoxyethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	671.2
100370		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(3-fluoro-4-pyridinyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(3-fluoro-4-pyridinyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	694.0
100371		(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(4-(4-morpholinyl)-1-butyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(4-(4-morpholinyl)-1-butyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	738.3
100372		(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(4-(4-morpholinyl)-1-butyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(4-(4-morpholinyl)-1-butyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-	738.5

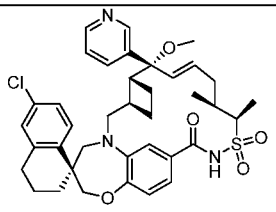
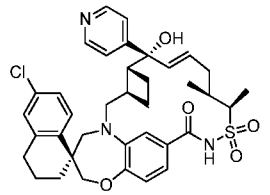
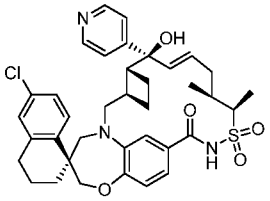
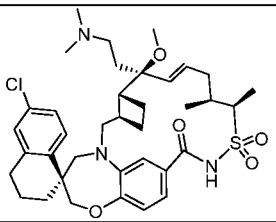
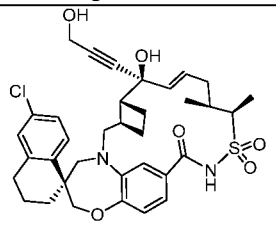
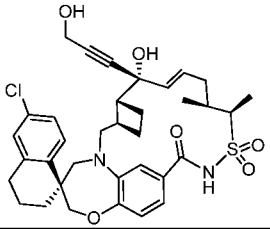
		[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	
100373		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(3-methyl-2-oxobutyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	719.3 (M+Na)
100374		2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N-cyclopropyl-N-methylacetamide	746.3
100375		2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N-methyl-N-(2,2,2-trifluoroethyl)acetamide	788.3 (M+Na)
100376		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-(4-methyl-1-piperazinyl)-2-oxoethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	753.3 (M+Na)
100377		2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N-methyl-N-(2-(4-morpholinyl)ethyl)acetamide	797.3

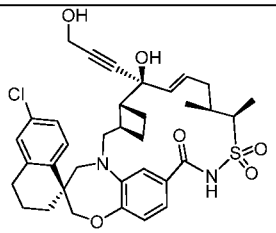
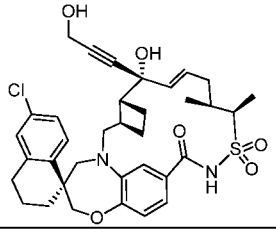
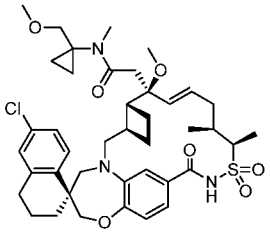
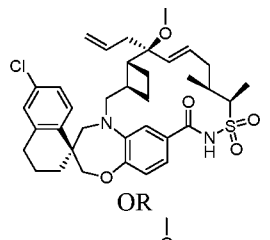
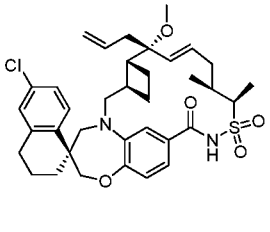
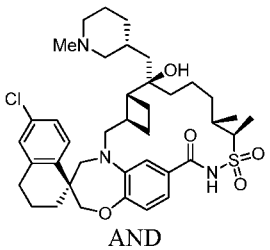
100378		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(methoxymethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	643.2
100379	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-pyrazinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-pyrazinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	659.0
100380		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	724.2
100381		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(2-(dimethylamino)ethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	684.3
100382	 AND	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(1-methyl-4-piperidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(1-methyl-4-piperidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	698.3

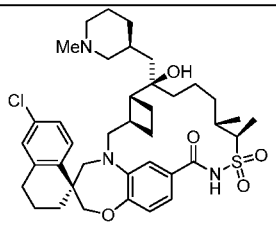
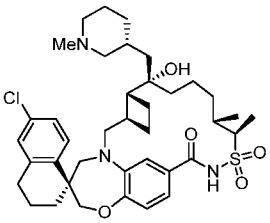
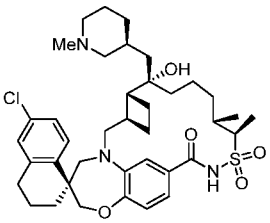
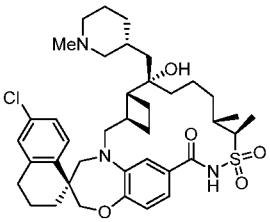
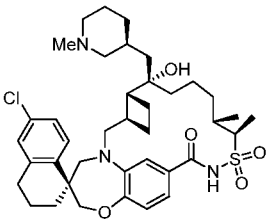
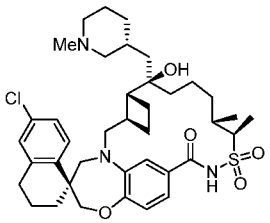
			
100383	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-pyrazinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-pyrazinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	677.0
100384	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(3-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(3-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	676.2
100385	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(3-fluoro-2-pyridinyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(3-fluoro-2-pyridinyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.	694.3

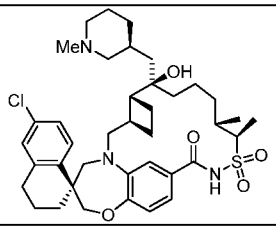
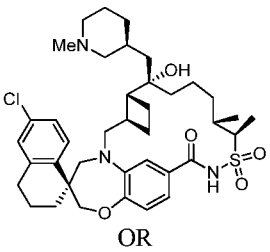
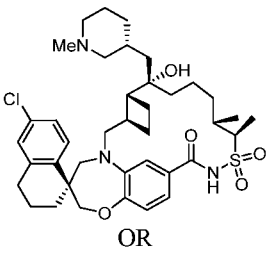
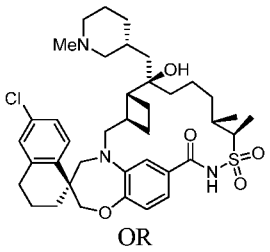
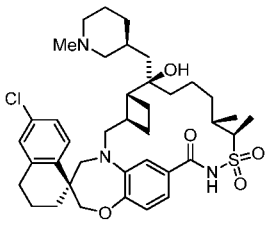
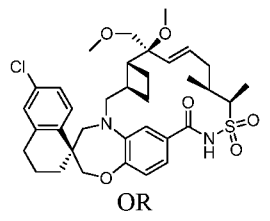
		7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100386	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(1-methyl-4-piperidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(1-methyl-4-piperidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	698.3
100387	 OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(1-methyl-4-piperidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(1-methyl-4-piperidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	698.3
100388	 OR	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(3-(1,1-dioxido-4-thiomorpholinyl)-1-propyn-1-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(3-(1,1-dioxido-4-thiomorpholinyl)-1-propyn-1-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.	770.4

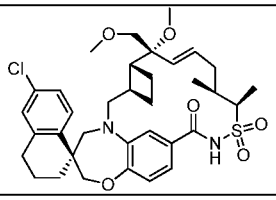
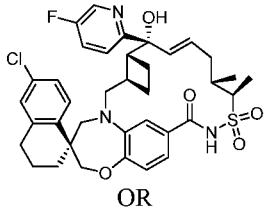
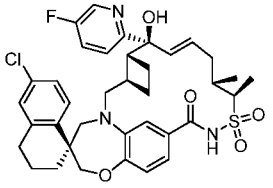
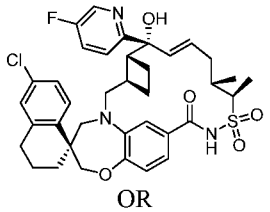
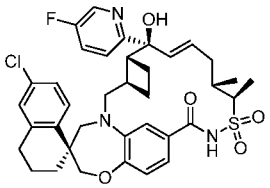
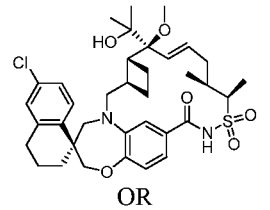
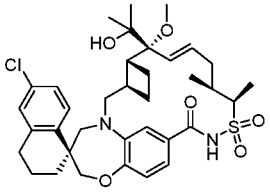
		7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100389	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(3-(1,1-dioxido-4-thiomorpholinyl)-1-propyn-1-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(3-(1,1-dioxido-4-thiomorpholinyl)-1-propyn-1-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	770.3
100390	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(3-fluoro-2-pyridinyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(3-fluoro-2-pyridinyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	694.3
100391	 OR	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(3-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	690.2

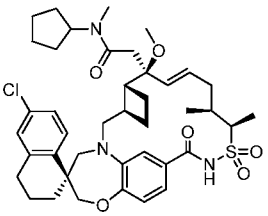
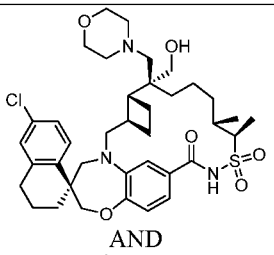
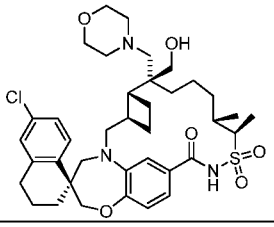
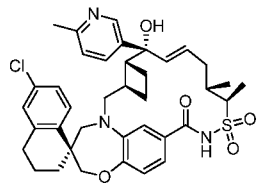
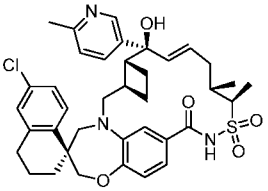
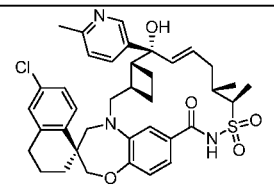
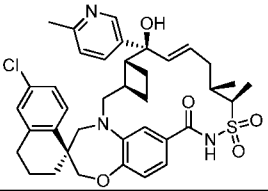
		OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(3-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100392	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(4-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(4-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	676.2
100393		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-(dimethylamino)ethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	684.2
100394	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(3-hydroxy-1-propyn-1-yl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(3-hydroxy-1-propyn-1-yl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	653.5

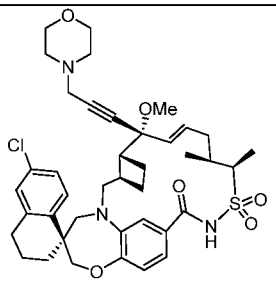
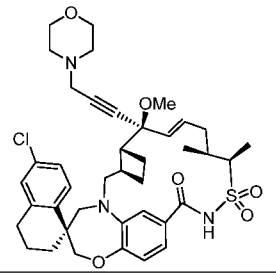
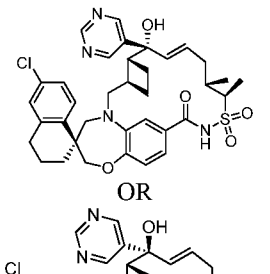
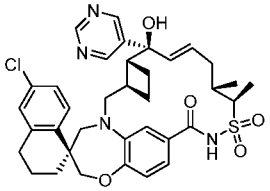
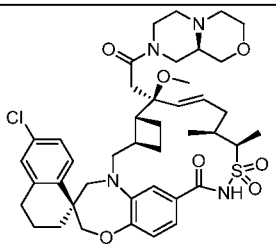
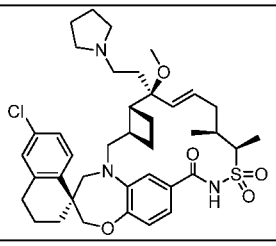
100395	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(3-hydroxy-1-propyn-1-yl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(3-hydroxy-1-propyn-1-yl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	653.3
100396		2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N-(1-(methoxymethyl)cyclopropyl)-N-methylacetamide	790.3 (M+Na)
100397	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-propen-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-propen-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	653.3
100398	 AND	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(((3R)-1-methyl-3-piperidinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(((3S)-1-	712.4

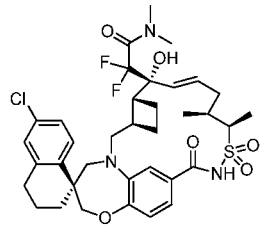
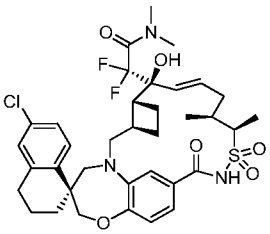
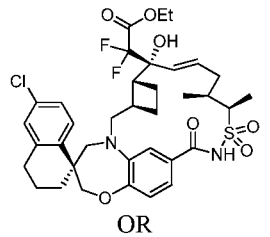
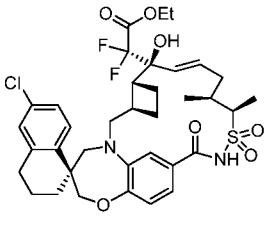
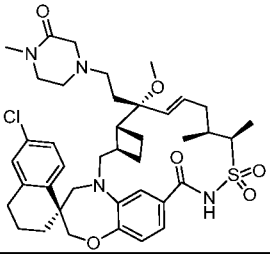
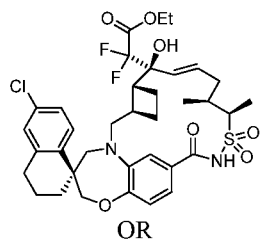
	 OR  AND 	methyl-3-piperidinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(((3R)-1-methyl-3-piperidinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(((3S)-1-methyl-3-piperidinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	
100399	 OR  OR  OR	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(((3R)-1-methyl-3-piperidinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(((3S)-1-methyl-3-piperidinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(((3R)-1-methyl-3-piperidinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(((3S)-1-	712.4

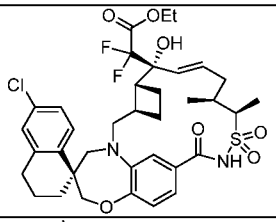
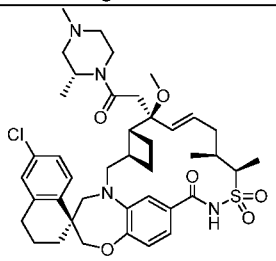
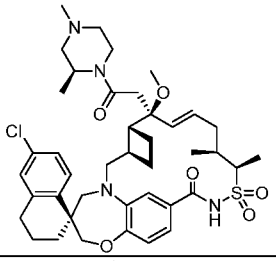
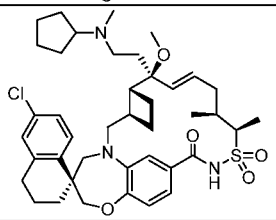
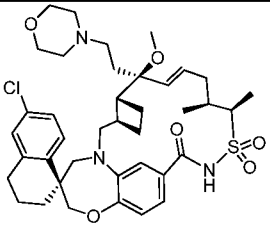
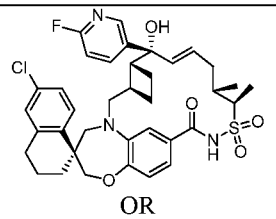
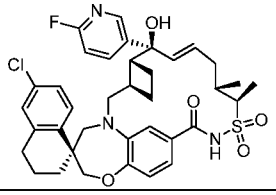
		methyl-3-piperidinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	
100400	 OR  OR  OR 	(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(((3S)-1-methyl-3-piperidinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(((3R)-1-methyl-3-piperidinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(((3R)-1-methyl-3-piperidinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(((3S)-1-methyl-3-piperidinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	712.4
100401	 OR	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-7'-(methoxymethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-7'-(methoxymethyl)-11',12'-	657.2

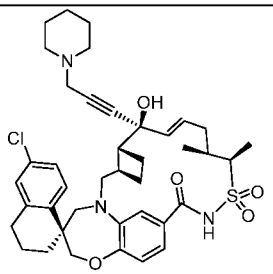
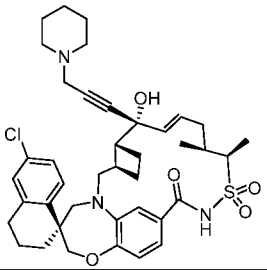
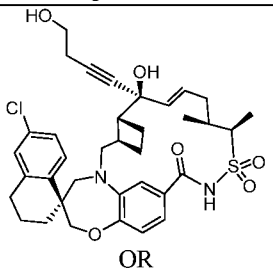
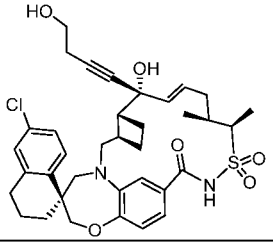
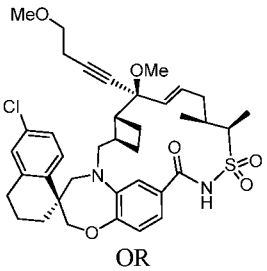
		dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100402	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(5-fluoro-2-pyridinyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(5-fluoro-2-pyridinyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	694.0
100403	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(5-fluoro-2-pyridinyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(5-fluoro-2-pyridinyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	694.0
100404	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-hydroxy-2-propanyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(2-hydroxy-2-propanyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	671.3

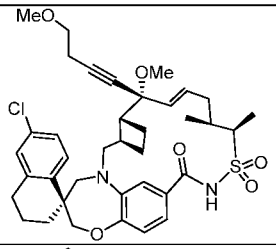
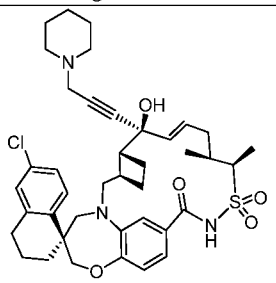
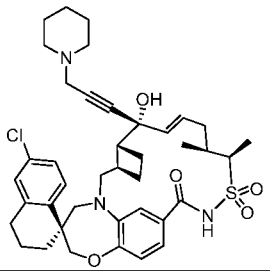
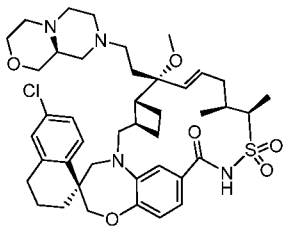
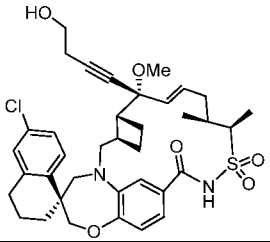
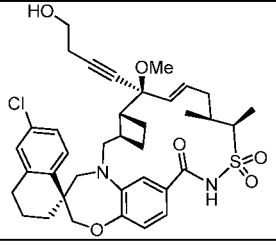
100405		2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N-cyclopentyl-N-methylacetamide	774.3 (M+Na)
100406	 AND 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-(hydroxymethyl)-11',12'-dimethyl-7'-(4-morpholinylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-(hydroxymethyl)-11',12'-dimethyl-7'-(4-morpholinylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	714.3
100407	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(6-methyl-3-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(6-methyl-3-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	690.0
100408	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(6-methyl-3-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(6-methyl-3-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.	690.0

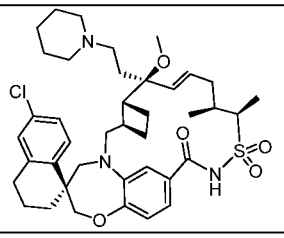
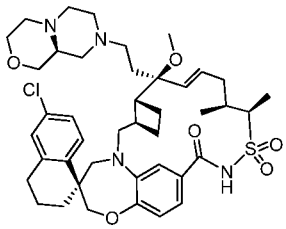
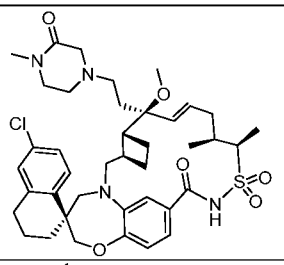
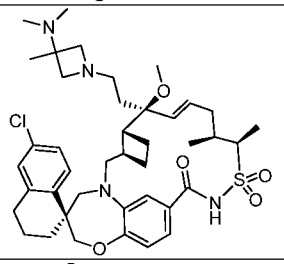
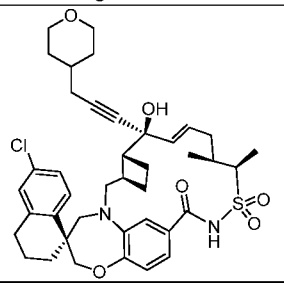
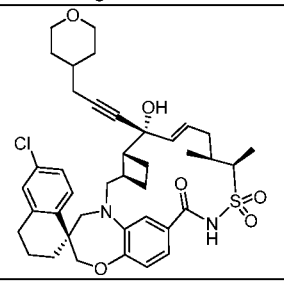
		7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100409	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(3-(4-morpholinyl)-1-propyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(3-(4-morpholinyl)-1-propyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	736.3
100410	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(5-pyrimidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(5-pyrimidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	677.2
100411		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-((9aR)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-2-oxoethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	795.2
100412		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-(1-pyrrolidinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	710.3

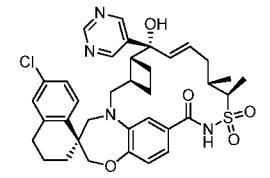
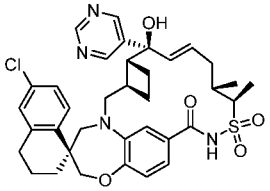
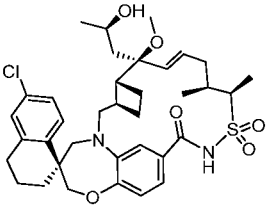
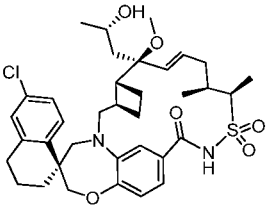
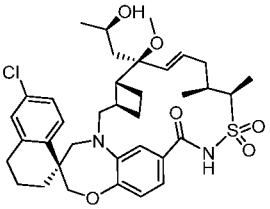
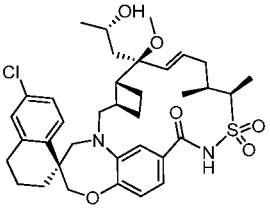
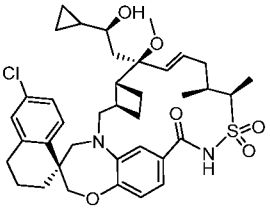
100413	 OR 	2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-2,2-difluoro-N,N-dimethylacetamide OR 2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-2,2-difluoro-N,N-dimethylacetamide	720.0
100414	 OR 	ethyl ((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)(difluoro)acetate OR ethyl ((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)(difluoro)acetate	721.0
100415		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-(4-methyl-3-oxo-1-piperazinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	775.3 (M+Na)
100416	 OR	ethyl ((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)(difluoro)acetate OR ethyl ((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-	721.0

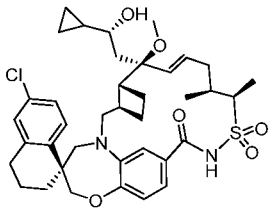
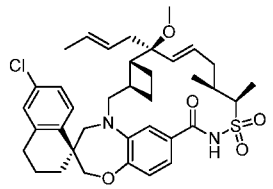
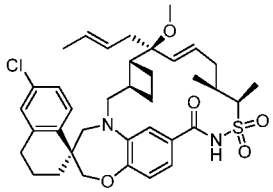
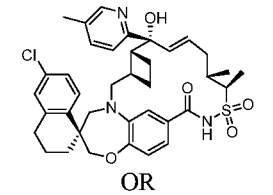
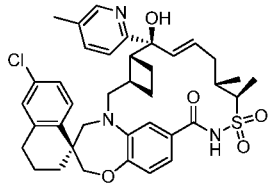
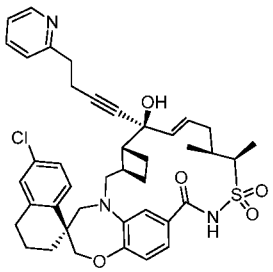
		spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)(difluoro)acetate	
100417	 AND 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-((2R)-2,4-dimethyl-1-piperazinyl)-2-oxoethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-((2S)-2,4-dimethyl-1-piperazinyl)-2-oxoethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	789.3 (M+Na)
100418		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-(cyclopentyl(methyl)amino)ethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	738.3
100419		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-(4-morpholinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	726.3
100420	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(6-fluoro-3-pyridinyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(6-fluoro-3-pyridinyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.	676.0

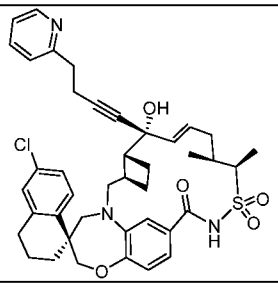
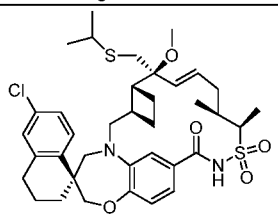
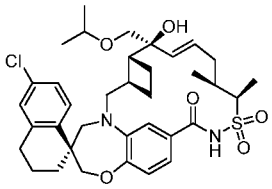
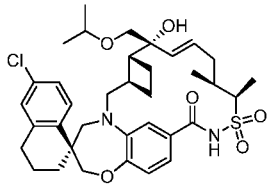
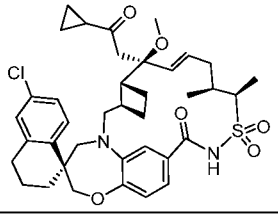
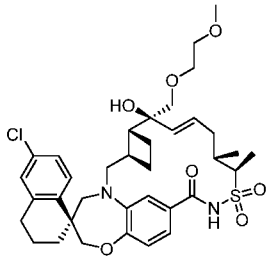
		7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100421	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(3-(1-piperidinyl)-1-propyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(3-(1-piperidinyl)-1-propyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	720.3
100422	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(4-hydroxy-1-butyn-1-yl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(4-hydroxy-1-butyn-1-yl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	667.4
100423	 OR	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-7'-(4-methoxy-1-butyn-1-yl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-7'-(4-methoxy-1-butyn-1-yl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	695.3

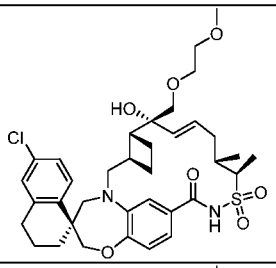
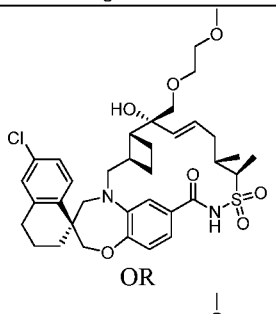
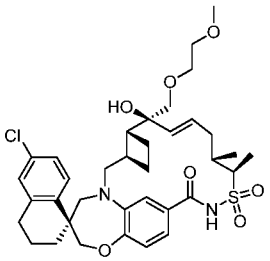
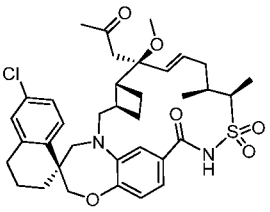
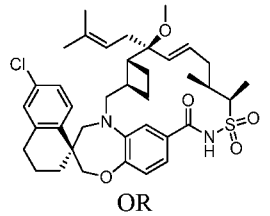
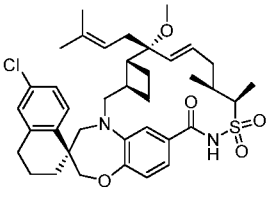
			
100424	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(3-(1-piperidinyl)-1-propyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(3-(1-piperidinyl)-1-propyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	720.3
100425		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(2-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)ethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	781.4
100426		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(4-hydroxy-1-butyn-1-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	681.3
100427		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(4-hydroxy-1-butyn-1-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	681.3

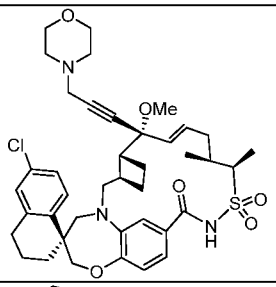
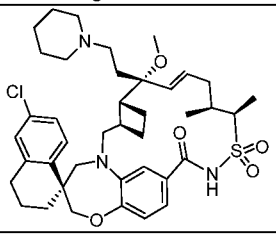
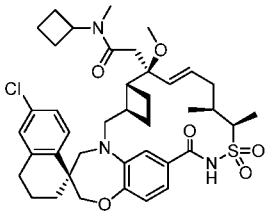
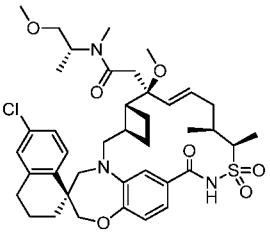
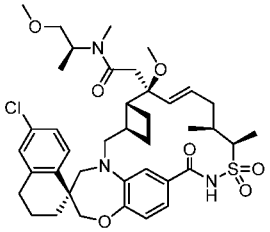
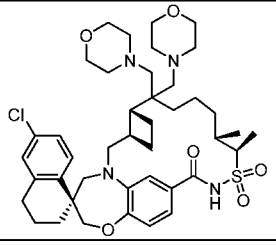
100428		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-(1-piperidinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	724.2
100429		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)ethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	781.4
100430		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-(4-methyl-3-oxo-1-piperazinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	753.3
100431		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-(3-(dimethylamino)-3-methyl-1-azetidinyl)ethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	753.3
100432		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(3-(tetrahydro-2H-pyran-4-yl)-1-propyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	721.3
100433		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(3-(tetrahydro-2H-pyran-4-yl)-1-propyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	721.3

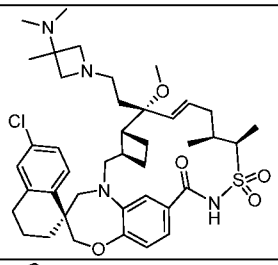
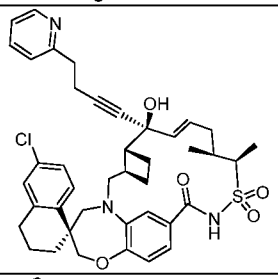
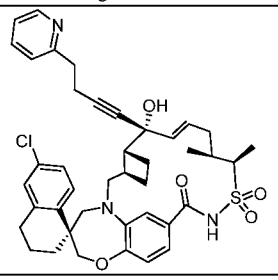
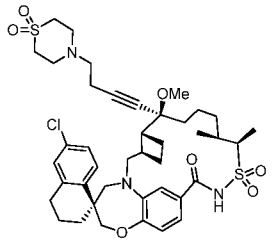
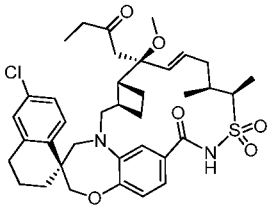
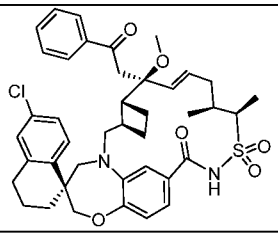
100434	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(5-pyrimidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(5-pyrimidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	677.2
100435	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((2R)-2-hydroxypropyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((2S)-2-hydroxypropyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	693.2 (M+Na)
100436	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((2R)-2-hydroxypropyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((2S)-2-hydroxypropyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	693.2 (M+Na)
100437		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((2R)-2-cyclopropyl-2-hydroxyethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	719.3 (M+Na)

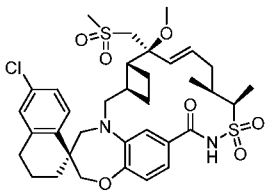
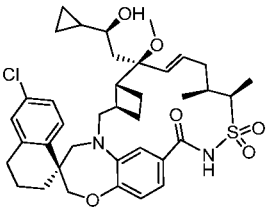
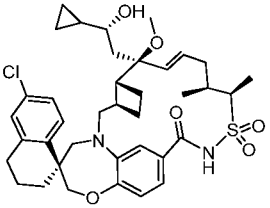
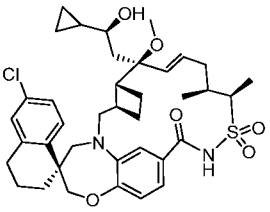
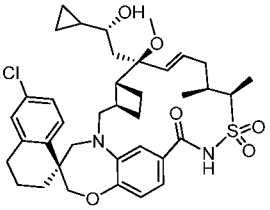
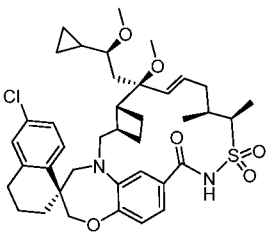
	AND 	AND (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((2S)-2-cyclopropyl-2-hydroxyethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100438	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-7'-((2E)-2-buten-1-yl)-6-chloro-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-7'-((2E)-2-buten-1-yl)-6-chloro-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	667.3
100439	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(5-methyl-2-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(5-methyl-2-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	690.2
100440	 AND	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(4-(2-pyridinyl)-1-butyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(4-(2-pyridinyl)-1-butyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	728.3

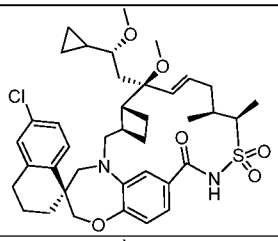
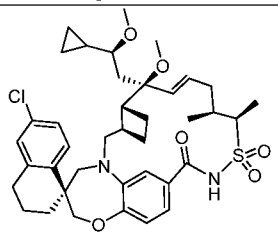
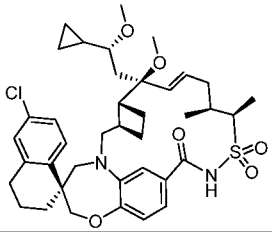
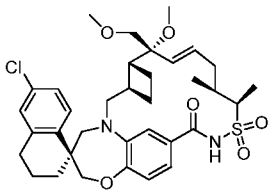
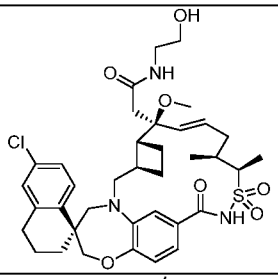
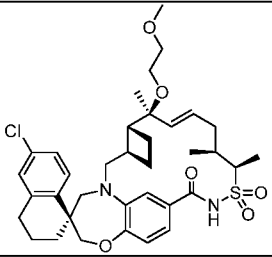
			
100441		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((2-propanylsulfanyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	723.2 (M+Na)
100442	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((2-propanyloxy)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((2-propanyloxy)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	671.3
100443		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-cyclopropyl-2-oxoethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	717.2 (M+Na)
100444	 OR	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-((2-methoxyethoxy)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-((2-methoxyethoxy)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.	687.2

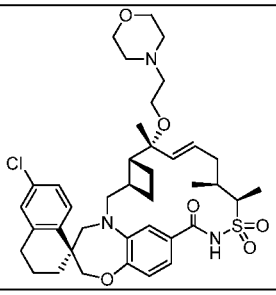
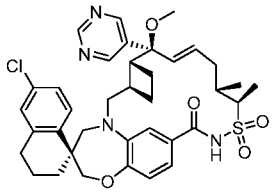
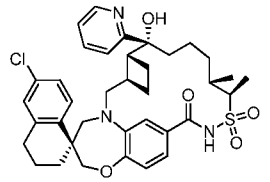
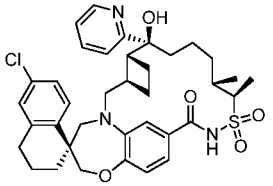
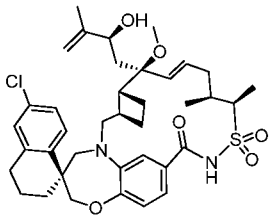
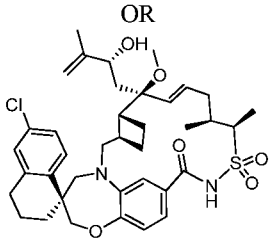
		7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100445	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-((2-methoxyethoxy)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-((2-methoxyethoxy)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	687.2
100446		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-oxopropyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	691.2 (M+Na)
100447	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(3-methyl-2-buten-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(3-methyl-2-buten-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	681.2

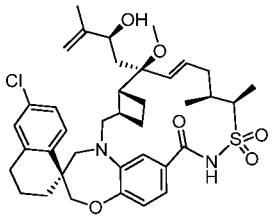
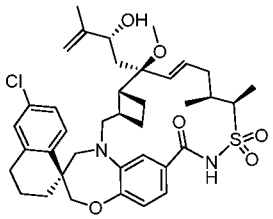
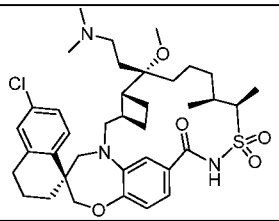
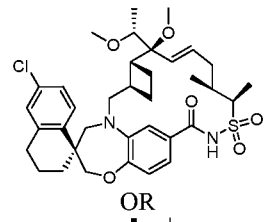
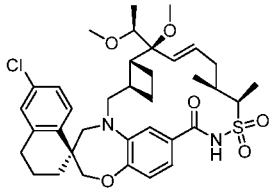
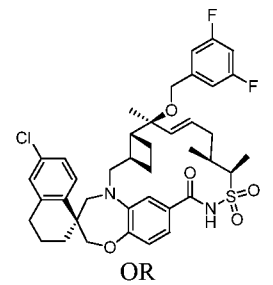
100448		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(3-(4-morpholinyl)-1-propyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	736.3
100449		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-(1-piperidinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	724.4
100450		2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N-cyclobutyl-N-methylacetamide	738.2
100451	 AND 	2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N-((2R)-1-methoxy-2-propanyl)-N-methylacetamide AND 2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N-((2S)-1-methoxy-2-propanyl)-N-methylacetamide	778.3 (M+Na)
100452		(1S,3'R,6'R,11'S,12'R)-6-chloro-11',12'-dimethyl-7',7'-bis(4-morpholinylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	783.5

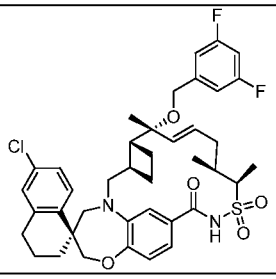
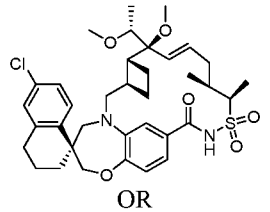
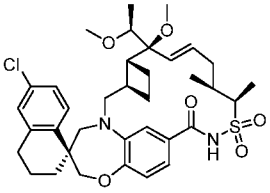
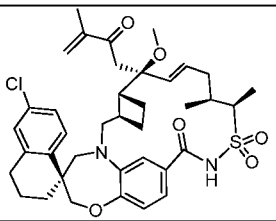
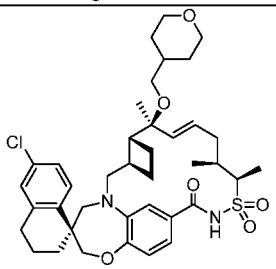
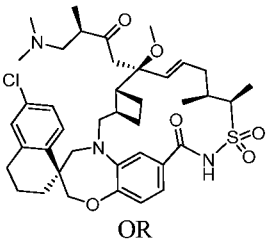
100453		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(2-(3-(dimethylamino)-3-methyl-1-azetidinyl)ethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	753.3
100454		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(4-(2-pyridinyl)-1-butyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	728.3
100455		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(4-(2-pyridinyl)-1-butyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	710.3 (M-H_2O]
100456		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(4-(1,1-dioxido-4-thiomorpholinyl)-1-butyn-1-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	798.3
100457		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-oxobutyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	705.2 (M+Na)
100458		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-oxo-2-phenylethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	753.2 (M+Na)

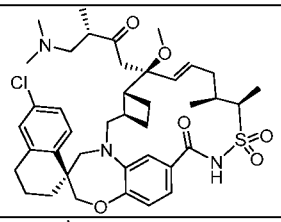
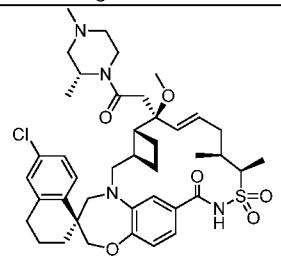
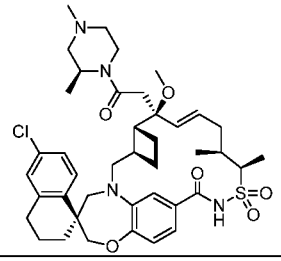
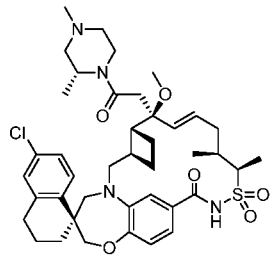
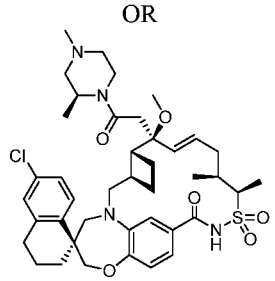
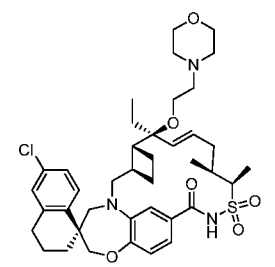
100459		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((methylsulfonyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	705.2
100460	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((2R)-2-cyclopropyl-2-hydroxyethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((2S)-2-cyclopropyl-2-hydroxyethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	697.2
100461	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((2R)-2-cyclopropyl-2-hydroxyethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((2S)-2-cyclopropyl-2-hydroxyethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	719.3 (M+Na)
100462	 OR	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((2S)-2-cyclopropyl-2-methoxyethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((2R)-2-cyclopropyl-2-methoxyethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	711.2

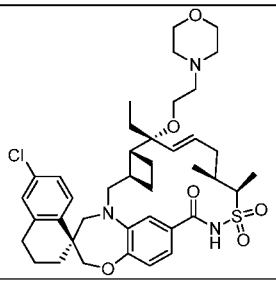
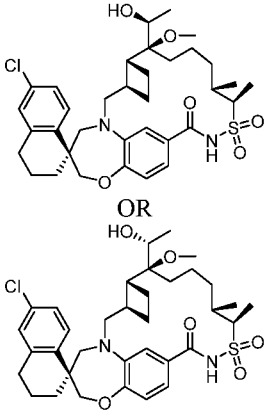
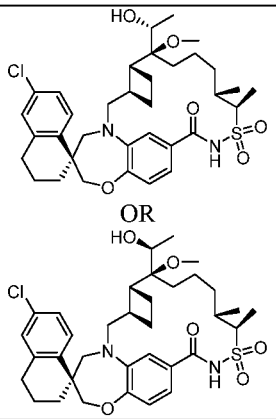
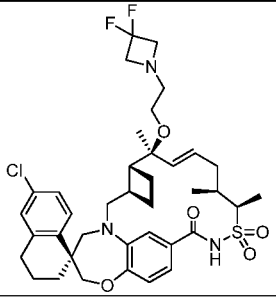
			
100463	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((2S)-2-cyclopropyl-2-methoxyethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((2R)-2-cyclopropyl-2-methoxyethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	733.3 (M+Na)
100464		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-7'-(methoxymethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	657.2
100465		2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N-(2-hydroxyethyl)acetamide	682.0 (M-OMe)
100466		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-methoxyethoxy)-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	671.3

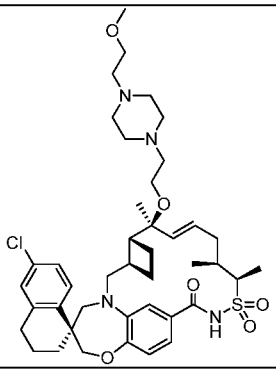
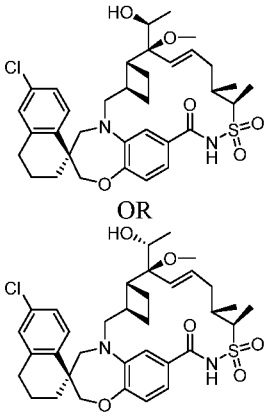
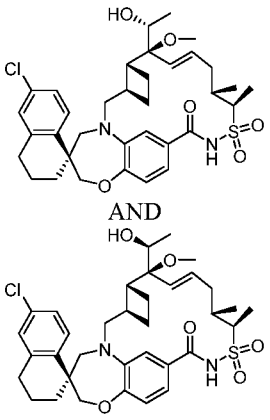
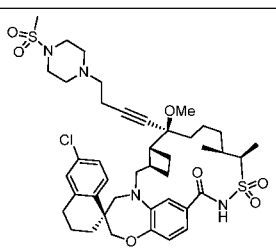
100467		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7',11',12'-trimethyl-7'-(2-(4-morpholinyl)ethoxy)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	726.3
100468		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(5-pyrimidinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	691.2
100469	 OR 	(1S,3'R,6'R,7'R,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	678.2
100470	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((2S)-2-hydroxy-3-methyl-3-buten-1-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((2R)-2-hydroxy-3-methyl-3-buten-1-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	697.2

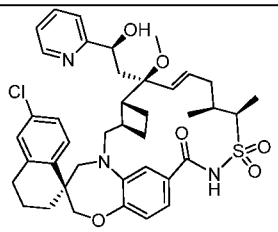
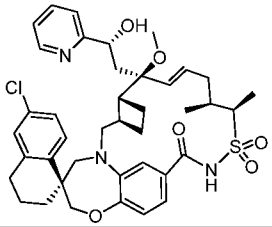
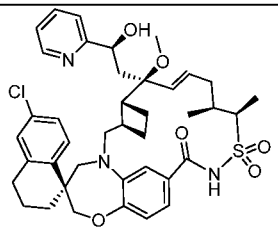
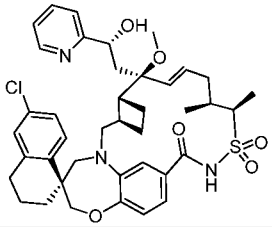
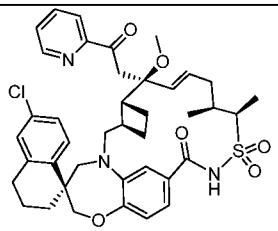
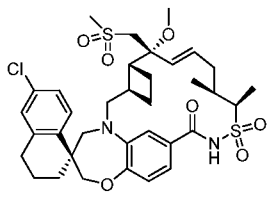
100471	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((2S)-2-hydroxy-3-methyl-3-buten-1-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((2R)-2-hydroxy-3-methyl-3-buten-1-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	697.2
100472		(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-(2-(dimethylamino)ethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	686.3
100473	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-7'-((1R)-1-methoxyethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-7'-((1S)-1-methoxyethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	671.3
100474	 OR	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((3,5-difluorobenzyl)oxy)-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((3,5-difluorobenzyl)oxy)-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.	739.2

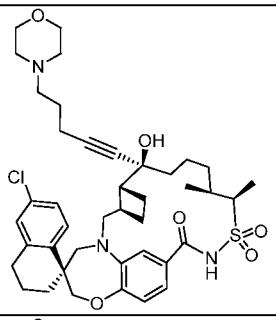
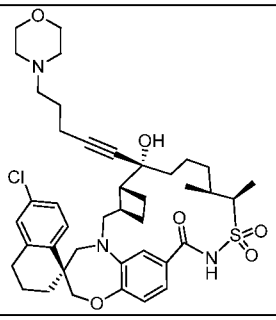
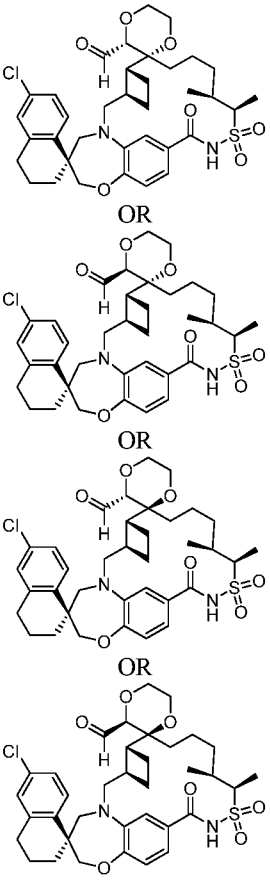
		7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100475	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-7'-((1R)-1-methoxyethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-7'-((1S)-1-methoxyethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	671.3
100476		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(3-methyl-2-oxo-3-buten-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	695.3
100477		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7',11',12'-trimethyl-7'-(tetrahydro-2H-pyran-4-ylmethoxy)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	711.3
100478	 OR	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((3R)-4-(dimethylamino)-3-methyl-2-oxobutyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((3S)-4-(dimethylamino)-3-methyl-2-oxobutyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-	740.3

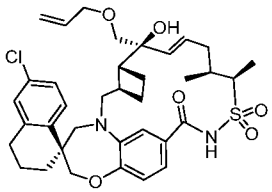
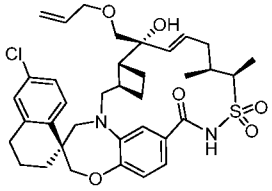
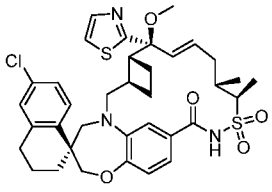
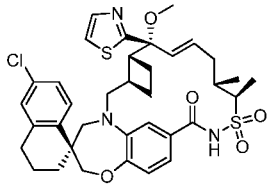
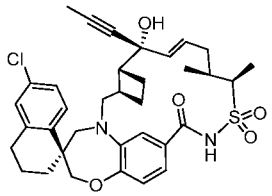
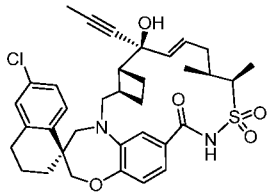
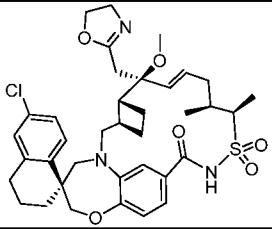
		1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100479	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-((2R)-2,4-dimethyl-1-piperazinyl)-2-oxoethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-((2S)-2,4-dimethyl-1-piperazinyl)-2-oxoethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	767.3
100480	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-((2S)-2,4-dimethyl-1-piperazinyl)-2-oxoethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-((2R)-2,4-dimethyl-1-piperazinyl)-2-oxoethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	767.3
100481	 OR	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethyl-11',12'-dimethyl-7'-(2-(4-morpholinyl)ethoxy)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR	740.3

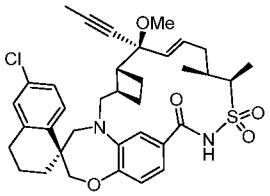
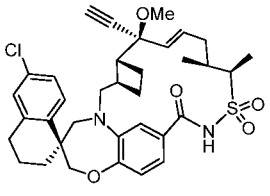
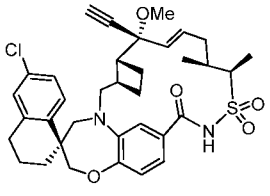
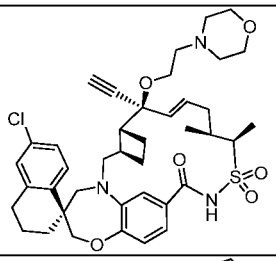
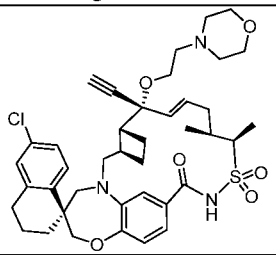
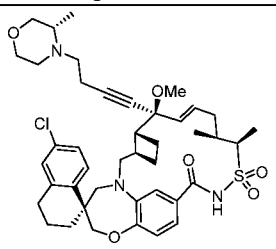
		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-ethyl-11',12'-dimethyl-7'-(2-(4-morpholinyl)ethoxy)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100482		(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-((1S)-1-hydroxyethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-((1R)-1-hydroxyethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	659.2
100483		(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-((1R)-1-hydroxyethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	659.2
100484		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-(3,3-difluoro-1-azetidinyl)ethoxy)-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	732.2

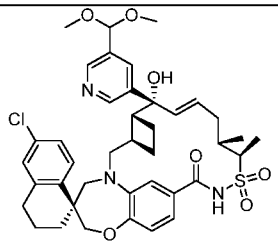
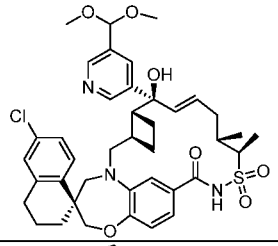
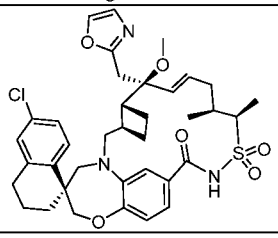
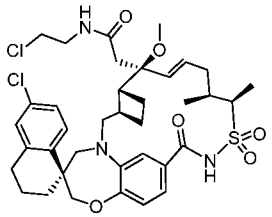
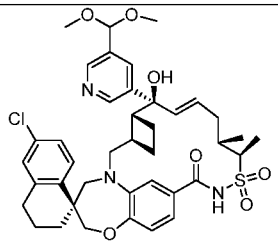
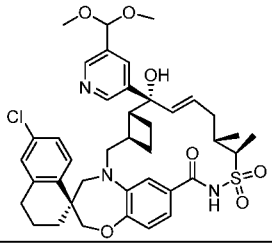
100485		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-(4-(2-methoxyethyl)-1-piperazinyl)ethoxy)-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	783.3
100486		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((1S)-1-hydroxyethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((1R)-1-hydroxyethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	657.3
100487		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((1R)-1-hydroxyethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((1S)-1-hydroxyethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	657.3
100488		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(4-(4-(methylsulfonyl)-1-piperazinyl)-1-butyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	827.2

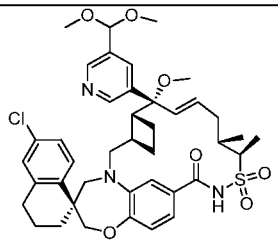
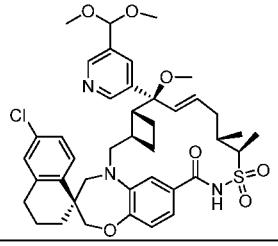
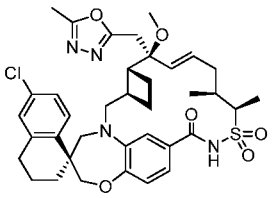
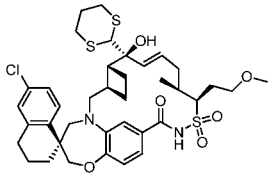
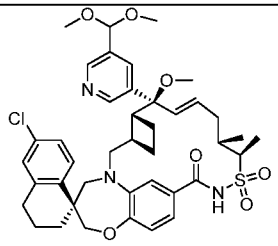
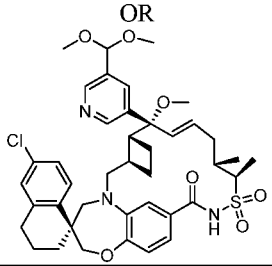
100489	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((2S)-2-hydroxy-2-(2-pyridinyl)ethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((2R)-2-hydroxy-2-(2-pyridinyl)ethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	734.3
100490	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((2S)-2-hydroxy-2-(2-pyridinyl)ethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((2R)-2-hydroxy-2-(2-pyridinyl)ethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	734.3
100491		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-oxo-2-(2-pyridinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	754.2 (M+Na)
100492		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((methylsulfonyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	705.2

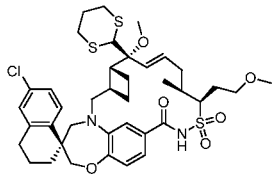
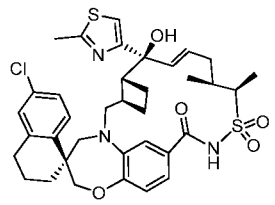
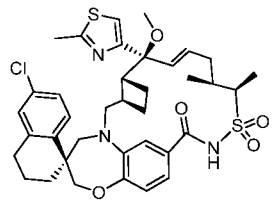
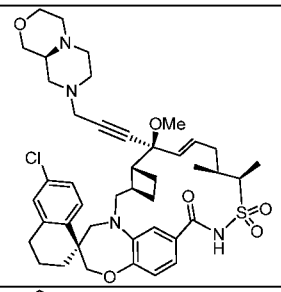
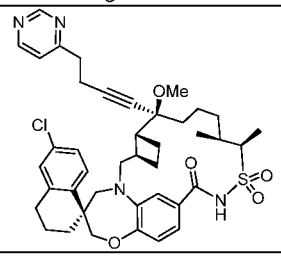
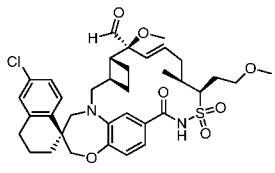
100493		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(5-(4-morpholinyl)-1-pentyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	750.3
100494		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(5-(4-morpholinyl)-1-pentyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	750.3
100495		(2R,3R,3'R,6'R,11'S,12'R,22'S)-6''-chloro-11',12'-dimethyl-15'-oxo-3'',4''-dihydro-2''H-dispiro[1,4-dioxane-2,7'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-22',1''-naphthalene]-3-carbaldehyde 13',13'-dioxide OR (2R,3S,3'R,6'R,11'S,12'R,22'S)-6''-chloro-11',12'-dimethyl-15'-oxo-3'',4''-dihydro-2''H-dispiro[1,4-dioxane-2,7'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-22',1''-naphthalene]-3-carbaldehyde 13',13'-dioxide OR (2S,3R,3'R,6'R,11'S,12'R,22'S)-6''-chloro-11',12'-dimethyl-15'-oxo-3'',4''-dihydro-2''H-dispiro[1,4-dioxane-2,7'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-22',1''-naphthalene]-3-carbaldehyde 13',13'-dioxide OR (2S,3S,3'R,6'R,11'S,12'R,22'S)-6''-chloro-11',12'-dimethyl-15'-oxo-3'',4''-dihydro-2''H-dispiro[1,4-dioxane-2,7'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]triene-22',1''-naphthalene]-3-carbaldehyde 13',13'-dioxide	685.3

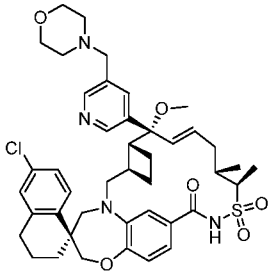
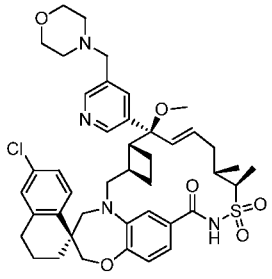
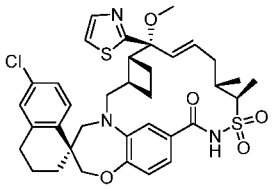
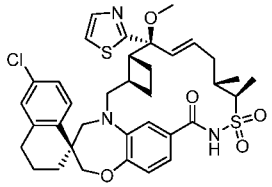
100496	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((2-propen-1-yloxy)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((2-propen-1-yloxy)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	669.2
100497	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(1,3-thiazol-2-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(1,3-thiazol-2-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	696.0
100498		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(1-propyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	637.4
100499		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(1-propyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	637.3
100500		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(4,5-dihydro-1,3-oxazol-2-ylmethyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	696.2

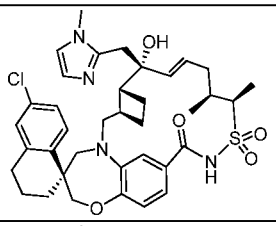
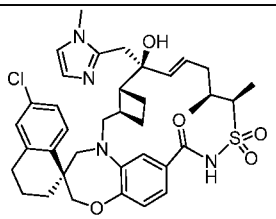
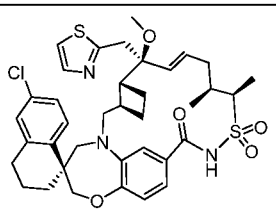
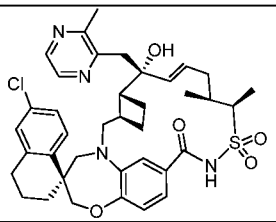
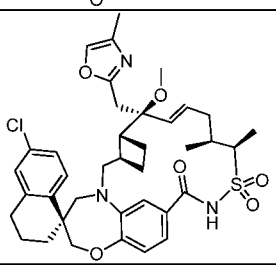
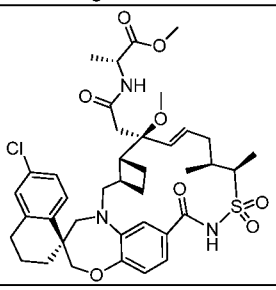
100501		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(1-propyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	651.2
100502		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-ethynyl-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	637.3
100503		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethynyl-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	637.3
100504		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-ethynyl-11',12'-dimethyl-7'-(2-(4-morpholinyl)ethoxy)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	736.2
100505		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethynyl-11',12'-dimethyl-7'-(2-(4-morpholinyl)ethoxy)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	736.2
100506		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(4-((3S)-3-methyl-4-morpholinyl)-1-butyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	764.2

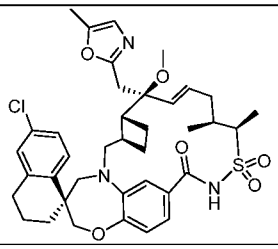
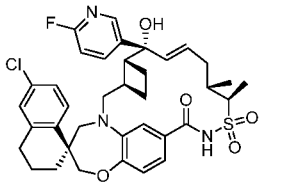
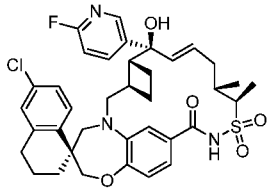
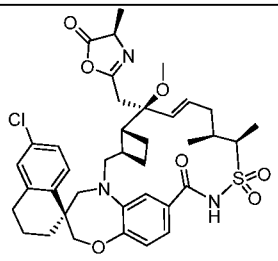
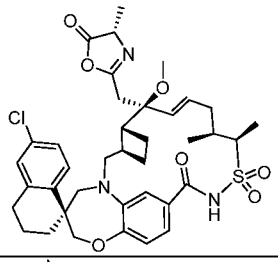
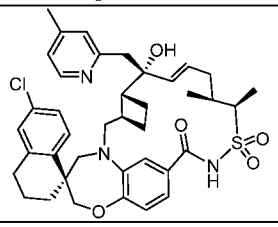
100507	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(5-(dimethoxymethyl)-3-pyridinyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(5-(dimethoxymethyl)-3-pyridinyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	750.0
100508		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(1,3-oxazol-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	694.3
100509		N-(2-chloroethyl)-2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetamide	754.2 (M+Na)
100510	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(5-(dimethoxymethyl)-3-pyridinyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(5-(dimethoxymethyl)-3-pyridinyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	750.0

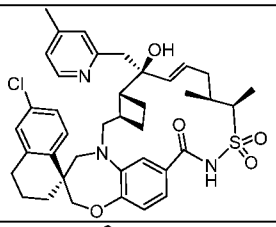
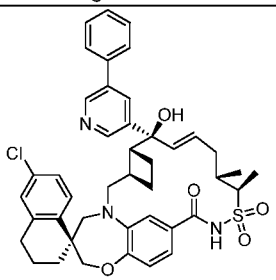
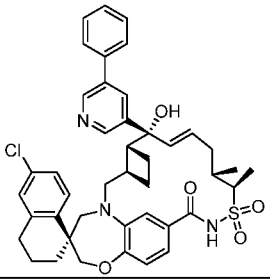
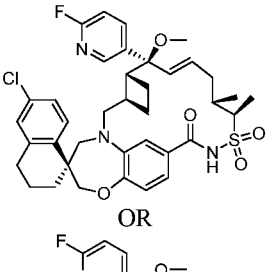
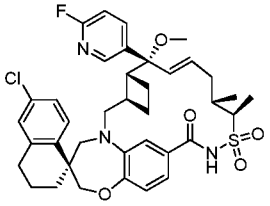
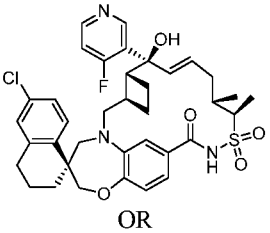
100511	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(5-(dimethoxymethyl)-3-pyridinyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(5-(dimethoxymethyl)-3-pyridinyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	764.2
100512		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((5-methyl-1,3,4-oxadiazol-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	709.2
100513		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-hydroxy-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	761.0
100514	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(5-(dimethoxymethyl)-3-pyridinyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(5-(dimethoxymethyl)-3-pyridinyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	764.2

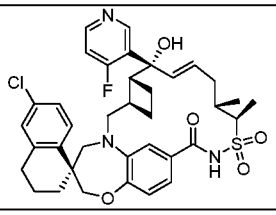
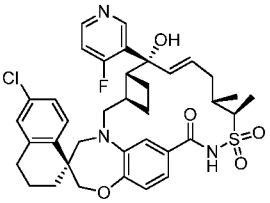
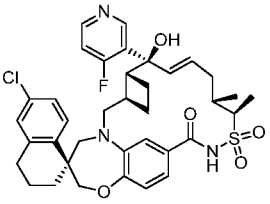
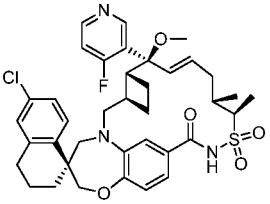
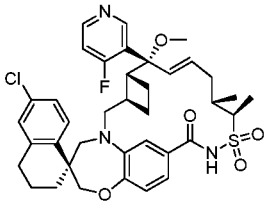
100515		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	775.1
100516		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(2-methyl-1,3-thiazol-4-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	695.8
100517		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-methyl-1,3-thiazol-4-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	710.0
100518		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(3-((9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-1-propyn-1-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	791.3
100519		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(4-(4-pyrimidinyl)-1-butyn-1-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	743.2
100520		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide	685.1

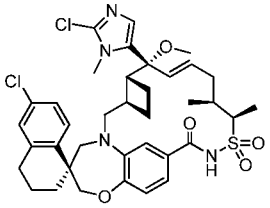
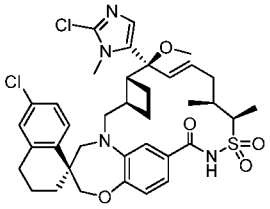
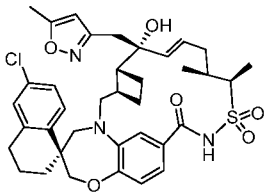
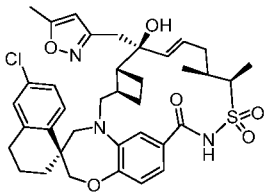
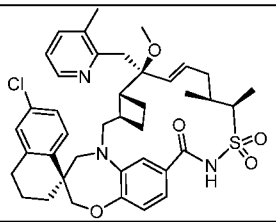
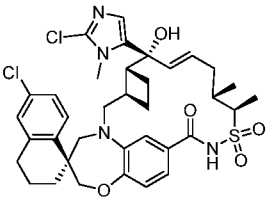
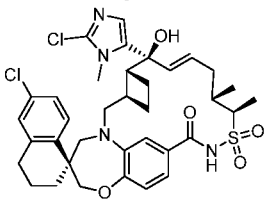
100521	 AND 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(5-(4-morpholinylmethyl)-3-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide|(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(5-(4-morpholinylmethyl)-3-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(5-(4-morpholinylmethyl)-3-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide|(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(5-(4-morpholinylmethyl)-3-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	789.2
100522	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(1,3-thiazol-2-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(1,3-thiazol-2-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	696.0

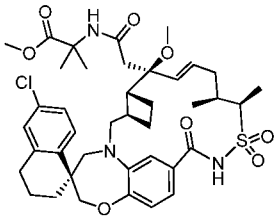
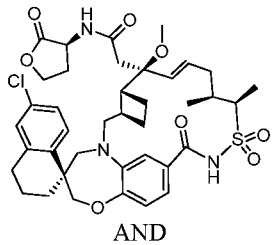
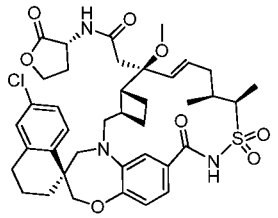
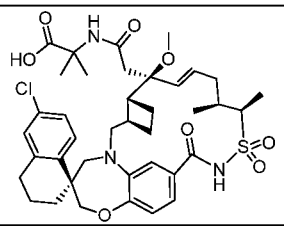
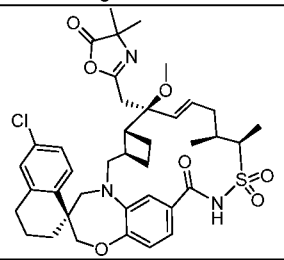
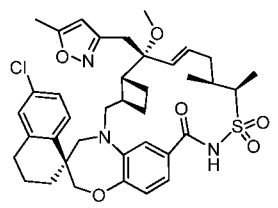
100523		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((1-methyl-1H-imidazol-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	693.0
100524		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((1-methyl-1H-imidazol-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	693.0
100525		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(1,3-thiazol-2-ylmethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	710.0
100526		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((3-methyl-2-pyrazinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	705.0
100527		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-methyl-1,3-oxazol-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	708.2
100528		methyl N-(((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetyl)-D-alaninate	778.3 (M+Na)

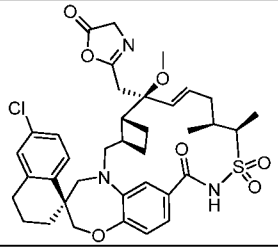
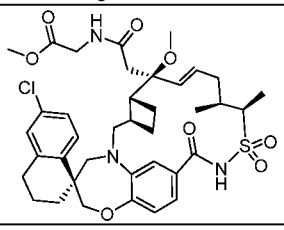
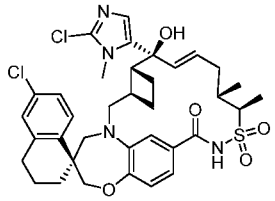
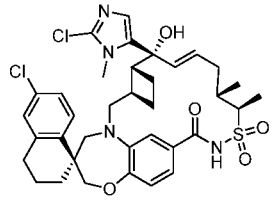
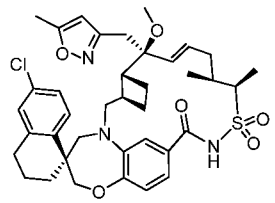
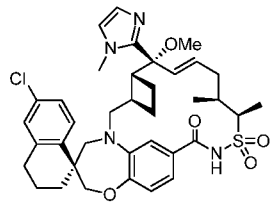
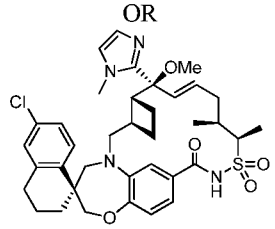
100529		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((5-methyl-1,3-oxazol-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	708.2
100530	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(6-fluoro-3-pyridinyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(6-fluoro-3-pyridinyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	676.0
100531	 AND 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((4R)-4-methyl-5-oxo-4,5-dihydro-1,3-oxazol-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(((4S)-4-methyl-5-oxo-4,5-dihydro-1,3-oxazol-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	724.2
100532		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((4-methyl-2-pyridinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	704.0

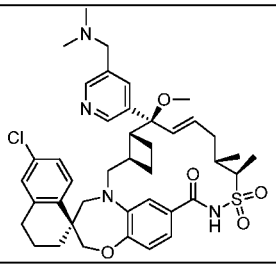
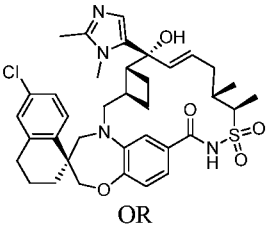
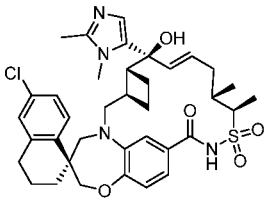
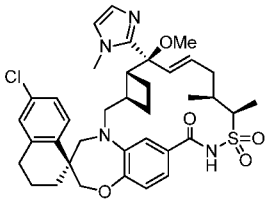
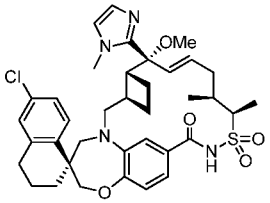
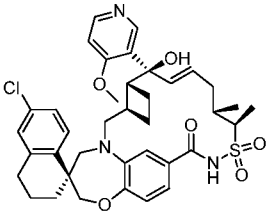
100533		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((4-methyl-2-pyridinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	704.0
100534	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(5-phenyl-3-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-(5-phenyl-3-pyridinyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	752.2
100535	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(6-fluoro-3-pyridinyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(6-fluoro-3-pyridinyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	676.0
100536	 OR	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(4-fluoro-3-pyridinyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(4-fluoro-3-pyridinyl)-7'-hydroxy-11',12'-	694.0

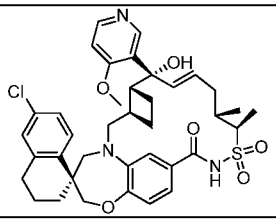
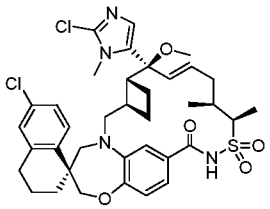
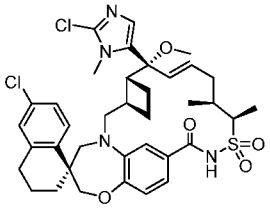
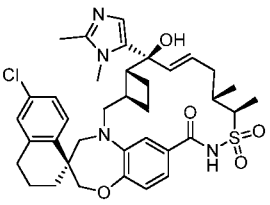
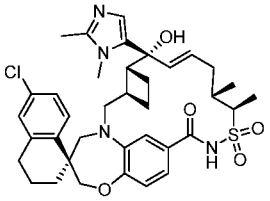
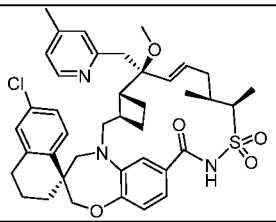
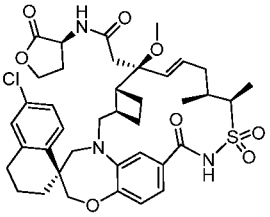
		dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100537	 AND 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(4-fluoro-3-pyridinyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide|(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(4-fluoro-3-pyridinyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide AND (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(4-fluoro-3-pyridinyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide|(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(4-fluoro-3-pyridinyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	694.0
100538	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(4-fluoro-3-pyridinyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(4-fluoro-3-pyridinyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	708.0

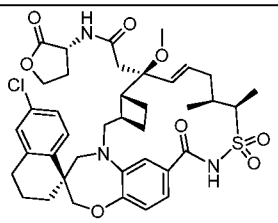
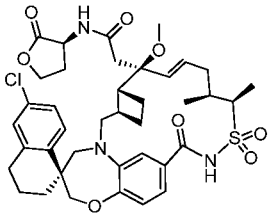
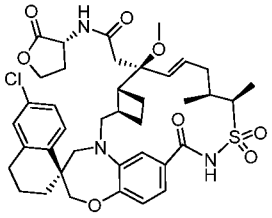
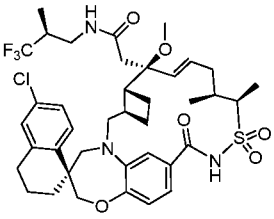
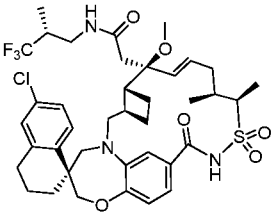
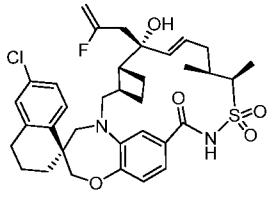
100539	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(2-chloro-1-methyl-1H-imidazol-5-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-chloro-1-methyl-1H-imidazol-5-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	727.2
100540		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((5-methyl-1,2-oxazol-3-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	694.0
100541		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((5-methyl-1,2-oxazol-3-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	694.0
100542		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((3-methyl-2-pyridinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	718.0
100543	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(2-chloro-1-methyl-1H-imidazol-5-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-chloro-1-methyl-1H-imidazol-5-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	713.2

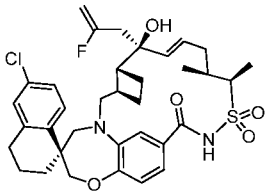
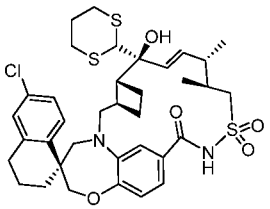
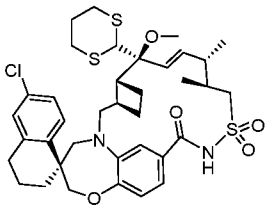
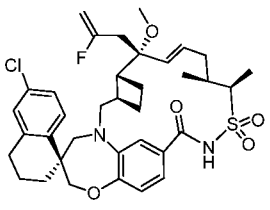
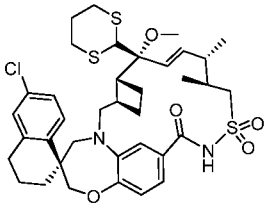
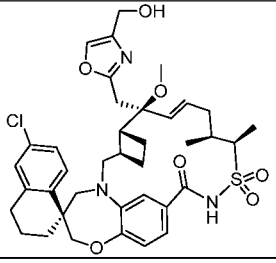
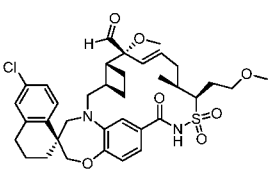
100544		methyl N-(((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetyl)-2-methylalaninate	738.2 (M-OMe)
100545	 AND 	2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N-((3R)-2-oxotetrahydro-3-furanyl)acetamide AND 2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N-((3S)-2-oxotetrahydro-3-furanyl)acetamide	722.3 (M-OMe)
100546		N-(((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetyl)-2-methylalanine	724.2 (M-OMe)
100547		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((4,4-dimethyl-5-oxo-4,5-dihydro-1,3-oxazol-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	738.2
100548		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((5-methyl-1,2-oxazol-3-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	708.0

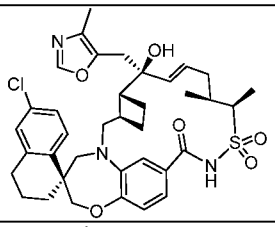
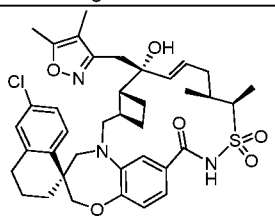
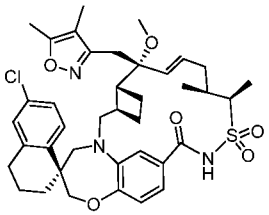
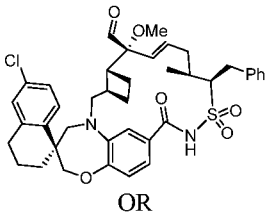
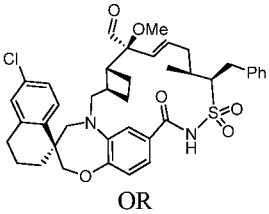
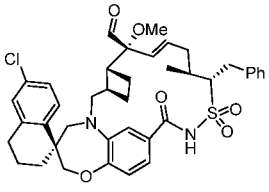
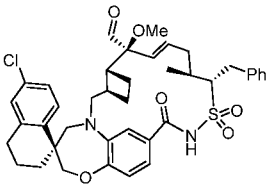
100549		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((5-oxo-4,5-dihydro-1,3-oxazol-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	710.3
100550		methyl N-(((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetyl)glycinate	710.3 (M-OMe)
100551	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-chloro-1-methyl-1H-imidazol-5-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(2-chloro-1-methyl-1H-imidazol-5-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	713.2
100552		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((5-methyl-1,2-oxazol-3-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	708.0
100553	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(1-methyl-1H-imidazol-2-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(1-methyl-1H-imidazol-2-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	693.2

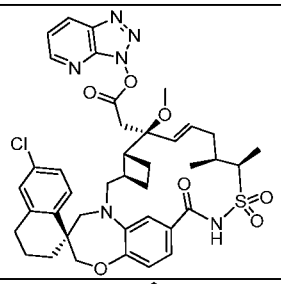
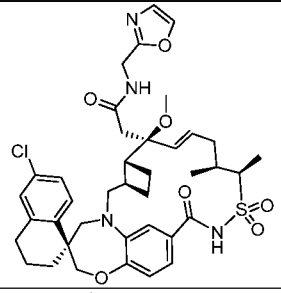
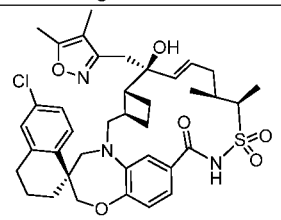
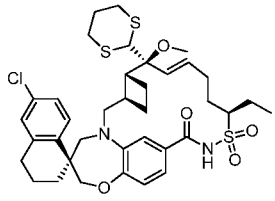
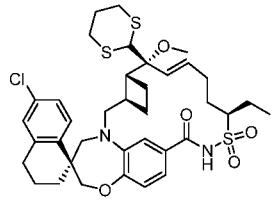
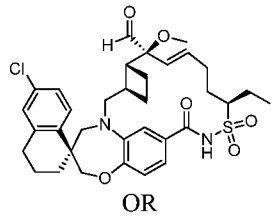
100554		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(5-((dimethylamino)methyl)-3-pyridinyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	747.2
100555	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(1,2-dimethyl-1H-imidazol-5-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(1,2-dimethyl-1H-imidazol-5-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	693.2
100556	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(1-methyl-1H-imidazol-2-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(1-methyl-1H-imidazol-2-yl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	693.2
100557	 OR	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(4-methoxy-3-pyridinyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7'-(4-methoxy-3-pyridinyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.	706.2

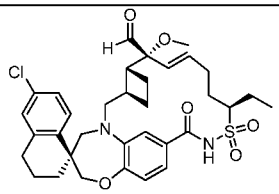
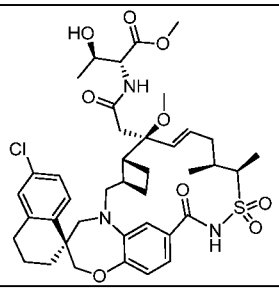
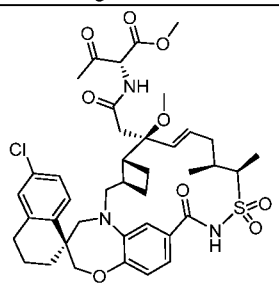
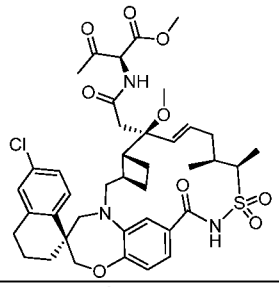
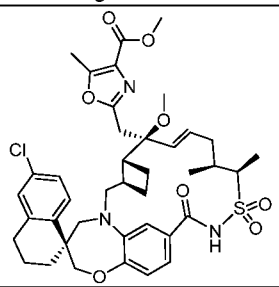
		7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100558	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-chloro-1-methyl-1H-imidazol-5-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(2-chloro-1-methyl-1H-imidazol-5-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	727.1
100559	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(1,2-dimethyl-1H-imidazol-5-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(1,2-dimethyl-1H-imidazol-5-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	693.2
100560		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((4-methyl-2-pyridinyl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	718.0
100561	 OR	2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N-((3R)-2-oxotetrahydro-3-furanyl)acetamide	722.2 (M-OMe)

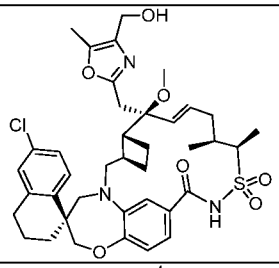
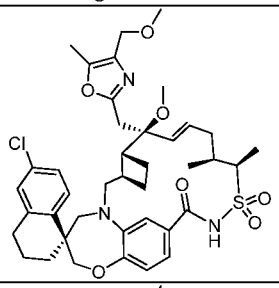
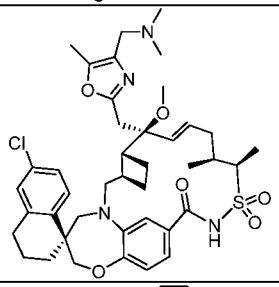
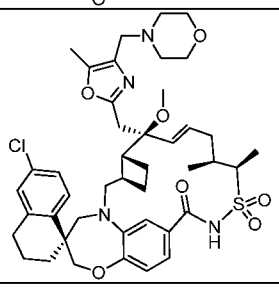
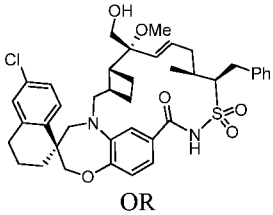
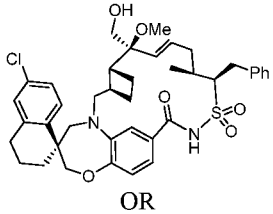
		OR 2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N-((3S)-2-oxotetrahydro-3-furanyl)acetamide	
100562	 OR 	2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N-((3R)-2-oxotetrahydro-3-furanyl)acetamide OR 2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N-((3S)-2-oxotetrahydro-3-furanyl)acetamide	722.2 (M-OMe)
100563	 AND 	2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N-((2R)-3,3,3-trifluoro-2-hydroxypropyl)acetamide AND 2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N-((2S)-3,3,3-trifluoro-2-hydroxypropyl)acetamide	750.2 (M-OMe)
100564		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(2-fluoro-2-propen-1-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	657.0

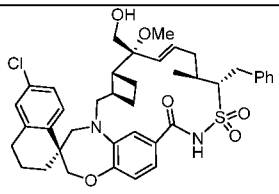
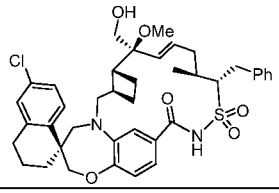
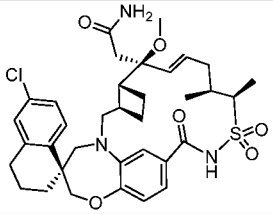
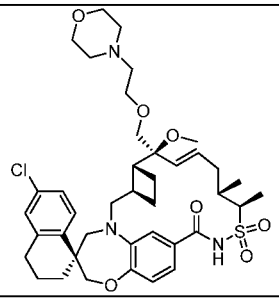
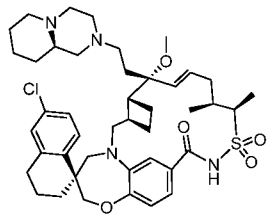
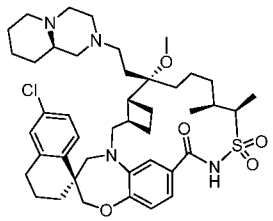
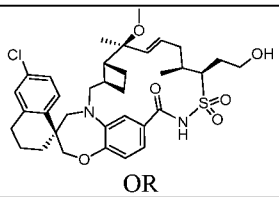
100565		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(2-fluoro-2-propen-1-yl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	657.0
100566		(1S,3'R,6'R,7'S,8'E,10'S,11'S)-6-chloro-7'-(1,3-dithian-2-yl)-7'-hydroxy-10',11'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	717.0
100567		(1S,3'R,6'R,7'S,8'E,10'S,11'S)-6-chloro-7'-(1,3-dithian-2-yl)-7'-methoxy-10',11'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	731.0
100568		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(2-fluoro-2-propen-1-yl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	671.0
100569		(1S,3'R,6'R,7'R,8'E,10'S,11'S)-6-chloro-7'-(1,3-dithian-2-yl)-7'-methoxy-10',11'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	731.0
100570		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((4-(hydroxymethyl)-1,3-oxazol-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	724.2
100571		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-12'-(2-methoxyethyl)-11'-methyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide	685.1

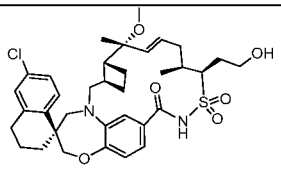
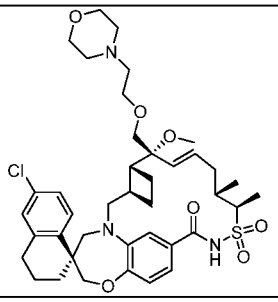
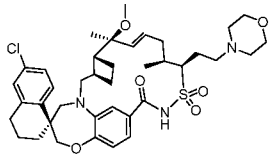
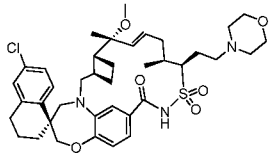
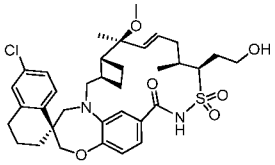
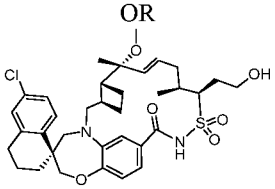
100572		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-7'-((4-methyl-1,3-oxazol-5-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	694.8
100573		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((4,5-dimethyl-1,2-oxazol-3-yl)methyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	708.0
100574		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-((4,5-dimethyl-1,2-oxazol-3-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	722.0
100575	 OR  OR  OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-12'-benzyl-6-chloro-7'-methoxy-11'-methyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-12'-benzyl-6-chloro-7'-methoxy-11'-methyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'S)-12'-benzyl-6-chloro-7'-methoxy-11'-methyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'S)-12'-benzyl-6-chloro-7'-methoxy-11'-methyl-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.	717.5

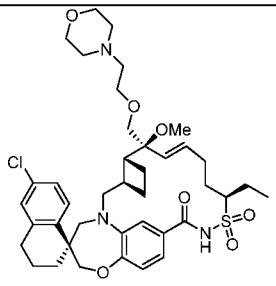
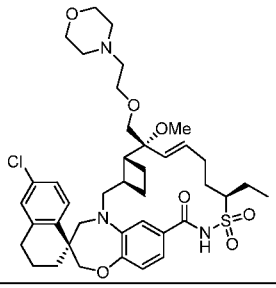
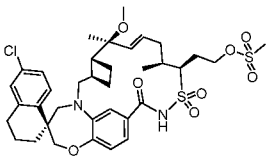
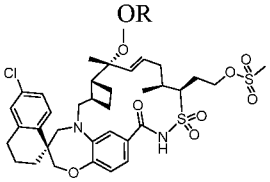
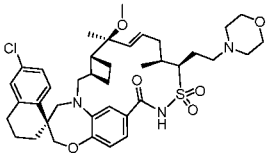
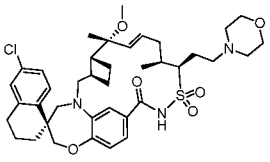
		7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide	
100576		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-oxo-2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yloxy)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	789.2
100577		2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)-N-(1,3-oxazol-2-ylmethyl)acetamide	719.3 (M-OMe)
100578		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((4,5-dimethyl-1,2-oxazol-3-yl)methyl)-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	708.0
100579	 OR 	(1S,3'R,6'R,7'S,8'E,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-12'-ethyl-7'-methoxy-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,12'R)-6-chloro-7'-(1,3-dithian-2-yl)-12'-ethyl-7'-methoxy-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	731.2
100580	 OR	(1S,3'R,6'R,7'S,8'E,12'R)-6-chloro-12'-ethyl-7'-methoxy-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide OR	641.2

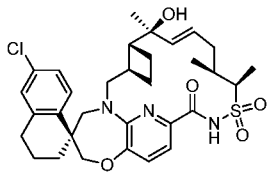
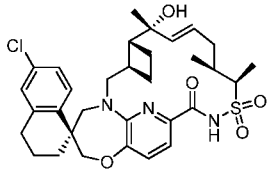
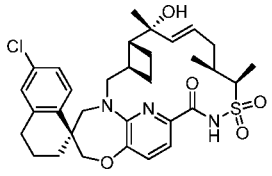
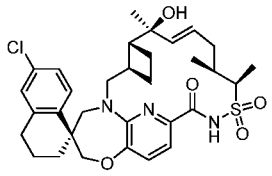
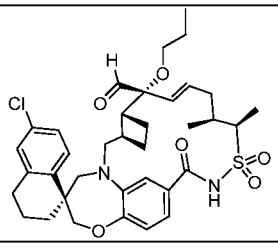
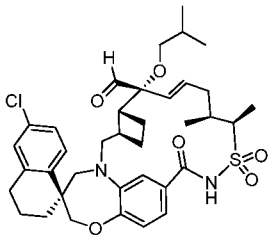
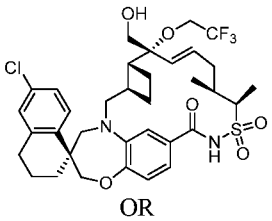
		(1S,3'R,6'R,7'R,8'E,12'R)-6-chloro-12'-ethyl-7'-methoxy-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide	
100581		methyl N-(((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetyl)-D-allothreoninate	754.2 (M-OMe)
100582	 AND 	methyl (2R)-2-((((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetyl)amino)-3-oxobutanoate AND methyl (2S)-2-((((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetyl)amino)-3-oxobutanoate	752.2 (M-OMe)
100583		methyl 2-(((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)methyl)-5-methyl-1,3-oxazole-4-carboxylate	766.3

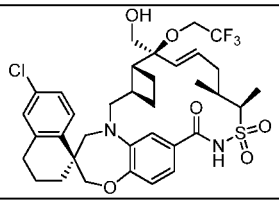
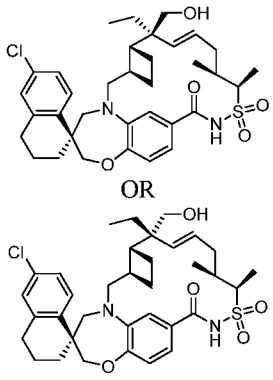
100584		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((4-(hydroxymethyl)-5-methyl-1,3-oxazol-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	738.2
100585		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-7'-((4-(methoxymethyl)-5-methyl-1,3-oxazol-2-yl)methyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	752.3
100586		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-((4-((dimethylamino)methyl)-5-methyl-1,3-oxazol-2-yl)methyl)-7'-methoxy-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	765.3
100587		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((5-methyl-4-(4-morpholinylmethyl)-1,3-oxazol-2-yl)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	807.3
100588	 OR  OR	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-12'-benzyl-6-chloro-7'-(hydroxymethyl)-7'-methoxy-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-12'-benzyl-6-chloro-7'-(hydroxymethyl)-7'-methoxy-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'S)-12'-benzyl-6-chloro-7'-(hydroxymethyl)-7'-	742.2 (M+Na)

	 OR 	methoxy-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'S)-12'-benzyl-6-chloro-7'-(hydroxymethyl)-7'-methoxy-11'-methyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100589		2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-7'-yl)acetamide	638.3 (M-OMe)
100590		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((2-(4-morpholinyl)ethoxy)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	756.2
100591		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-yl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	779.3
100592		(1S,3'R,6'R,7'S,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-(2-((9aR)-octahydro-2H-pyrido[1,2-a]pyrazin-2-yl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[16,18,24]trien]-15'-one 13',13'-dioxide	781.2
100593	 OR	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-12'-(2-hydroxyethyl)-7'-methoxy-7',11'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.	657.2

		7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-12'-(2-hydroxyethyl)-7'-methoxy-7',11'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100594		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-11',12'-dimethyl-7'-((2-(4-morpholinyl)ethoxy)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	756.2
100595	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-7',11'-dimethyl-12'-(2-(4-morpholinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-7',11'-dimethyl-12'-(2-(4-morpholinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	726.3
100596	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-12'-(2-hydroxyethyl)-7'-methoxy-7',11'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-12'-(2-hydroxyethyl)-7'-methoxy-7',11'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	657.2

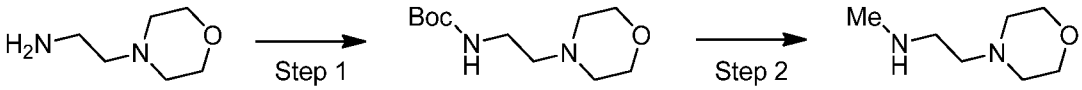
100597	 OR 	(1S,3'R,6'R,7'S,8'E,12'R)-6-chloro-12'-ethyl-7'-methoxy-7'-((2-(4-morpholinyl)ethoxy)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,12'R)-6-chloro-12'-ethyl-7'-methoxy-7'-((2-(4-morpholinyl)ethoxy)methyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	756.2
100598	 OR 	2-((1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-7',11'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-12'-yl)ethyl methanesulfonate OR 2-((1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-7',11'-dimethyl-13',13'-dioxido-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-12'-yl)ethyl methanesulfonate	703.3 (M-OMe)
100599	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-methoxy-7',11'-dimethyl-12'-(2-(4-morpholinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-methoxy-7',11'-dimethyl-12'-(2-(4-morpholinyl)ethyl)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	726.2

100600	 OR 	(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	614.0
100601	 OR 	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-7',11',12'-trimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14,25]triazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	614.0
100602		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-15'-oxo-7'-propoxy-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide	669.3
100603		(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-11',12'-dimethyl-7'-(2-methylpropoxy)-15'-oxo-3,4-dihydro-2H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraene]-7'-carbaldehyde 13',13'-dioxide	683.3
100604	 OR	(1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-(hydroxymethyl)-11',12'-dimethyl-7'-(2,2,2-trifluoroethoxy)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-(hydroxymethyl)-11',12'-dimethyl-7'-	711.2

		(2,2,2-trifluoroethoxy)-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	
100605		(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-ethyl-7'-(hydroxymethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide OR (1S,3'R,6'R,7'R,8'E,11'S,12'R)-6-chloro-7'-ethyl-7'-(hydroxymethyl)-11',12'-dimethyl-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide	641.2

GENERAL SYNTHESIS OF INTERMEDIATES

N-Methyl-2-morpholinoethanamine



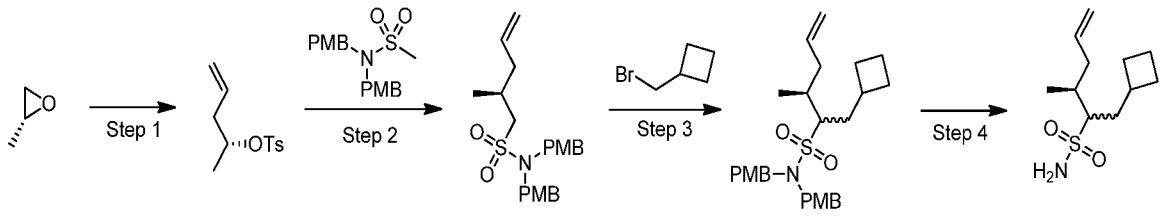
Step 1: tert-butyl (2-morpholinoethyl)carbamate

A 2-dram vial was charged with di-t-butyldicarbonate (0.459 mL, 2.000 mmol), a magnetic stir bar, and indium (III) chloride (4.42 mg, 0.020 mmol). 4-(2-Aminoethyl)morpholine (0.262 mL, 2 mmol) was then added to the stirring solution. After 1 min, the solution was diluted with EtOAc (2 mL). Water (3 mL) was added and the layers were partitioned. The organic layer was washed with water (2 x 5 mL), dried over $MgSO_4$, filtered, and concentrated to afford tert-butyl (2-morpholinoethyl)carbamate as a clear oil. The material was carried forward without further purification.

Step 2: N-methyl-2-morpholinoethanamine

A 125 mL three-neck flask with stir bar was heated with a heat gun under vacuum. Under a positive pressure of nitrogen, a reflux condenser was attached to the middle neck. The flask was charged with tetrahydrofuran (25.00 mL) and lithium aluminium hydride (2 M solution in THF, 0.84 mL, 20 mmol), tert-butyl (2-morpholinoethyl)carbamate (0.46 g, 2 mmol) was added as a solution in THF (8 mL) and the resulting homogenous mixture was heated to reflux for 18 h. The reaction mixture was cooled to 0 °C in an ice-water bath and quenched with sodium sulfate decahydrate. The resulting mixture was filtered through Celite, rinsing with THF. Concentration of the filtrate afforded N-methyl-2-morpholinoethanamine which was used without further purification.

(3S)-1-Cyclobutyl-3-methylhex-5-ene-2-sulfonamide



Step 1. (R)-pent-4-en-2-yl 4-methylbenzenesulfonate

To a solution of vinyl magnesium bromide (226 g, 1722 mmol, 1.0 M in THF) was added to CuI (29.5 g, 155 mmol, 0.09 equiv) in THF (200 mL) at –40 °C. The reaction mixture was stirred for 30 min followed by a cooled solution of (R)-2-methyloxirane (100 g, 1722 mmol) in THF (500 mL) was added drop wise at the same temperature. The resulting reaction mixture was stirred at –40 ° C for 1 h. After the reaction was completed (monitored by TLC), triethylamine (261 g, 2583 mmol) was added at –40 °C. After 30 min, cooled solution of p-toluene sulfonyl chloride (427 g, 2238 mmol) in THF (1000 mL) was added slowly to the reaction mixture at same temperature and stirred for 16 h at ambient temperature. After the reaction was completed (monitored by TLC), the reaction mixture was quenched with 1.5 N HCl solution until pH 3.0. The resulting reaction mixture was filtered through celite pad, layers were separated and the aqueous layer was re-extracted with ethyl acetate (2 x 2000 mL). The combined organic layers were washed with water (800 mL), brine (500 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified on flash column chromatography (silica gel, 230-400 mesh) using 1% to 2% ethyl acetate in petroleum ether to provide (R)-pent-4-en-2-yl 4-methylbenzenesulfonate (207 g, 50% yield) as a colourless liquid. ^{1}H NMR (300 MHz, Chloroform-d) δ 7.83 – 7.75 (m, 2H), 7.37 – 7.31 (m, 2H), 5.69 – 5.52 (m, 1H), 5.09 – 5.04 (m, 1H), 5.01 (t, J = 1.3 Hz, 1H), 4.65 (h, J = 6.3 Hz, 1H), 2.45 (s, 3H), 2.37 – 2.22 (m, 2H), 1.26 (d, J = 6.3 Hz, 3H).

Step 2: (S)-N,N-bis(4-methoxybenzyl)-2-methylpent-4-ene-1-sulfonamide

To a stirred solution of N,N-bis(4-methoxybenzyl)methanesulfonamide (207 g, 617 mmol) in THF (2000 mL) was added n-BuLi (321 mL, 802 mmol , 2.5

M in hexane) at –78 °C. The resulting reaction mixture was stirred for 1 h at same temperature followed by (R)-pent-4-en-2-yl 4-methylbenzenesulfonate (206 g, 858 mmol) in THF (400 mL) was added dropwise at –78 °C. The reaction mixture was allowed to warm to ambient temperature and stirred for 16 h. After the reaction was complete (monitored by TLC), the reaction mixture was quenched with saturated ammonium chloride solution, layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 2000 mL). The combined organic layers were washed with water (1000 mL), brine (600 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 230-400 mesh) using 2% to 4% ethyl acetate in petroleum ether to provide (S)-N,N-bis(4-methoxybenzyl)-2-methylpent-4-ene-1-sulfonamide (105 g, 42% yield) as a colourless liquid. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.25 – 7.20 (m, 4H), 6.92 – 6.85 (m, 4H), 5.70 (ddt, J = 17.2, 10.2, 7.1 Hz, 1H), 5.12 – 4.98 (m, 2H), 4.32 – 4.19 (m, 4H), 3.83 (s, 6H), 2.90 – 2.80 (m, 1H), 2.66 – 2.55 (m, 1H), 2.27 – 2.17 (m, 1H), 2.17 – 2.02 (m, 2H), 1.11 (d, J = 6.7, 3H).

Step 3. (3S)-1-cyclobutyl-N,N-bis(4-methoxybenzyl)-3-methylhex-5-ene-2-sulfonamide

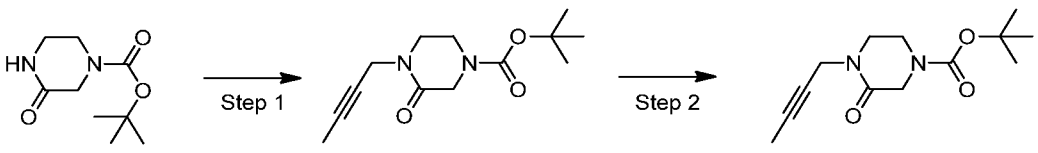
To a stirred solution of (S)-N,N-bis(4-methoxybenzyl)-2-methylpent-4-ene-1-sulfonamide (40 g, 99 mmol) in THF (400 mL) was added n-butyl lithium (86.73 mL, 139 mmol, 1.6 M in hexane) at –78 °C. The reaction mixture was allowed to stir for 20 min at same temperature. (Bromomethyl)cyclobutane (59.1 g, 396 mmol) was added dropwise at same temperature and stirred for 30 min. The resulting reaction mixture was allowed to warm to ambient temperature and stirred for 16 h. After the reaction was complete (monitored by TLC), the reaction mixture was quenched with saturated ammonium chloride solution, layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 400 mL). The combined organic layers were washed with water (100 mL), brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 230-400 mesh)

using 2% to 4% ethyl acetate in petroleum ether as an eluent to provide (3S)-1-cyclobutyl-N,N-bis(4-methoxybenzyl)-3-methylhex-5-ene-2-sulfonamide (33 g, 71% yield) as colourless liquid. ^{1}H NMR (300 MHz, Chloroform-d) δ 7.30 – 7.16 (m, 4H), 6.92 – 6.80 (m, 4H), 5.13 – 4.95 (m, 2H), 4.40 – 4.20 (m, 4H), 3.81 (s, 6H), 2.87 – 2.63 (m, 2H), 2.16 – 1.72 (m, 6H), 1.65 – 1.24 (m, 6H), 1.15 – 0.81 (m, 3H).

Step 4: (3S)-1-cyclobutyl-3-methylhex-5-ene-2-sulfonamide

To a stirred solution of (3S)-1-cyclobutyl-N,N-bis(4-methoxybenzyl)-3-methylhex-5-ene-2-sulfonamide (33 g, 70.0 mmol), anisole (33 mL) and TFA (33 mL) at 0 °C. The resulting reaction mixture was heated to 40 °C for 16 h. After the reaction was complete (monitored by TLC), volatiles were removed under vacuum and the crude was purified by flash column chromatography (silica gel, 230-400 mesh) using 15% to 20 % ethyl acetate in petroleum ether as an eluent to yield (3S)-1-cyclobutyl-3-methylhex-5-ene-2-sulfonamide which was further purified by HPLC [Column Sunfire C18 (250 mm x 19 mm) 5 µm, 0.1% formic acid in water and acetonitrile, 90 mg /injection, ELSD detector, run time 35 min.] to provide (3S)-1-cyclobutyl-3-methylhex-5-ene-2-sulfonamide (10.3 g, 64% yield) as a colourless liquid. MS (ESI, -ve ion) *m/z* 230 $(M-H)^-$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.78 (d, J = 9.1 Hz, 2H), 5.73 (tdd, J = 12.4, 10.1, 6.5 Hz, 1H), 5.05 (tt, J = 17.7, 4.5 Hz, 2H), 2.70 – 2.54 (m, 2H), 2.30 (p, J = 7.1 Hz, 1H), 2.00 (dq, J = 26.6, 7.3 Hz, 4H), 1.90 – 1.72 (m, 3H), 1.58 (dtt, J = 26.6, 17.4, 8.5 Hz, 3H), 0.94 (ddd, J = 14.1, 7.1, 2.1 Hz, 3H).

1-(But-2-yn-1-yl)piperazin-2-one



Step 1: tert-butyl 4-(but-2-yn-1-yl)-3-oxopiperazine-1-carboxylate

To a cooled (0 °C) slurry of 60% sodium hydride in mineral oil (0.600 g, 15.00 mmol) in THF (40 mL) was added a solution of 1-Boc-3-oxopiperazine (2.0 g, 9.99 mmol; Combi-Blocks, San Diego, CA) in N, N-dimethylformamide (10 mL). After complete addition the reaction was allowed to warm to room temperature for 30 min. The mixture was cooled to 0 °C and treated with 1-bromo-2-butyne (1.2 mL, 13.71 mmol). The reaction was allowed to warm to rt for 30 min. The reaction was quenched with saturated NH_4Cl solution, partitioned between EtOAc/brine and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give tert-butyl 4-(but-2-yn-1-yl)-3-oxopiperazine-1-carboxylate as a light-brown liquid.

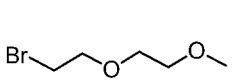
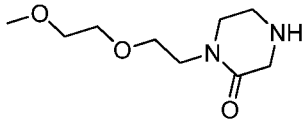
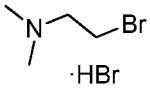
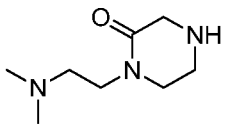
Step 2: 1-(but-2-yn-1-yl)piperazin-2-one

To a room temperature solution of tert-butyl 4-(but-2-yn-1-yl)-3-oxopiperazine-1-carboxylate (2.52 g, 9.99 mmol) in DCM (40 mL) was added trifluoroacetic acid (10 mL, 135 mmol) via syringe. After 1 h the solvent was removed in vacuo and the residue was dissolved in DCM. The solution was loaded onto an Si-propylsulfonic acid (Silicycle) cartridge eluting with DCM, MeOH then 2 M NH_3 in MeOH to give 1-(but-2-yn-1-yl)piperazin-2-one (1.269 g, 83% yield) as a brown oil. ^1H NMR (400 MHz, $CDCl_3$) δ 4.20 (q, *J*=2.41 Hz, 2 H), 3.52 (s, 2 H), 3.42 (t, *J*=5.48 Hz, 2 H), 3.12 (t, *J*=5.58 Hz, 2 H), 1.81 (t, *J*=2.45 Hz, 3 H).

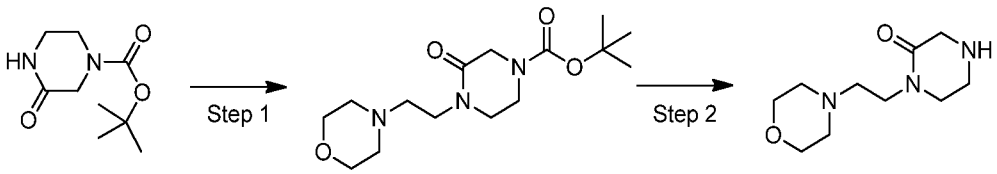
The intermediates shown in the following Table 3 were prepared analogous to the method described above for 1-(but-2-yn-1-yl)piperazin-2-one.

TABLE 3

Starting Material	Product	Name	MS Data $(M+1)^+$

		1-(2-(2-methoxyethoxy)ethyl)piperazin-2-one	203.3
 (Matrix Scientific)		1-(2-(dimethylamino)ethyl)piperazin-2-one	172.1

1-(2-Morpholinoethyl)piperazin-2-one



Step 1: tert-butyl 4-(2-morpholinoethyl)-3-oxopiperazine-1-carboxylate

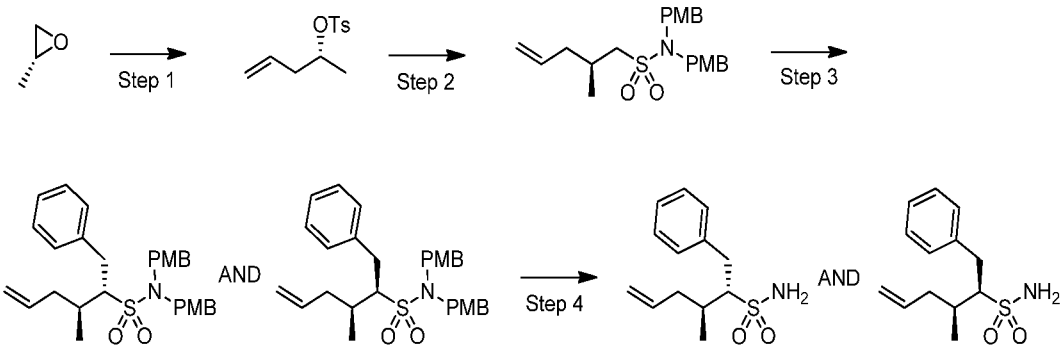
To a room temperature suspension of 1-boc-3-oxopiperazine (2.0 g, 9.99 mmol; Combi-Blocks, San Diego, CA), tetrabutylammonium bromide (0.620 g, 1.923 mmol) and potassium hydroxide (1.42 g, 25.3 mmol) in THF (25 mL) was added 4-(2-bromoethyl)morpholine hydrobromide (2.78 g, 10.11 mmol; Combi-Blocks, San Diego, CA) as a solid. After stirring at room temperature overnight the mixture was filtered and the filtrate was evaporated onto silica gel and purified by flash chromatography (Isco, (80 gram)) eluting with 2 M NH_3 in MeOH:CH_2Cl_2 (0:1 → 1:9) to give tert-butyl 4-(2-morpholinoethyl)-3-oxopiperazine-1-carboxylate (1.923 g , 61% yield) as a solid. MS (ESI, +ve ion) *m/z* 314.3 $(M+1)^+$.

Step 2: 1-(2-morpholinoethyl)piperazin-2-one

To a room temperature solution of tert-butyl 4-(2-morpholinoethyl)-3-oxopiperazine-1-carboxylate (1.84 g, 5.87 mmol) in DCM (15 mL) was added trifluoroacetic acid (5 mL). After 3 h the solvent was removed under reduced pressure and the residue was dissolved in DCM and loaded onto a plug of Si-

propylsulfonic acid (Silicycle) and the plug washed with 1:1 MeOH/DCM to 2 M NH_3 in MeOH/DCM. The fractions containing desired product were concentrated under reduced pressure to give 1-(2-morpholinoethyl)piperazin-2-one (1.52 g) as a yellow oil. MS (ESI, +ve ion) *m/z* 214.1 $(M+1)^+$.

(2S,3S)-3-Methyl-1-phenylhex-5-ene-2-sulfonamide AND (2R,3S)-3-methyl-1-phenylhex-5-ene-2-sulfonamide



Step 1: (R)-pent-4-en-2-yl 4-methylbenzenesulfonate

To a solution of vinyl magnesium bromide (226 g, 1722 mmol, 1.0 M in THF) was added to CuI (29.5 g, 155 mmol) in THF (200 mL) at – 40 °C. The reaction mixture was stirred for 30 min followed by a cooled solution of (R)-2-methyloxirane (100 g, 1722 mmol) in THF (500 mL) was added drop wise at the same temperature. The resulting reaction mixture was stirred at -40 ° C for 1 h. After the reaction was completed (monitored by TLC), triethylamine (261 g, 2583 mmol) was added at -40 °C. After 30 min, cooled solution of p-toluene sulfonyl chloride (427 g, 2238 mmol) in THF (1000 mL) was added slowly to the reaction mixture at same temperature and stirred for 16 h at ambient temperature. After the reaction was completed (monitored by TLC), the reaction mixture was quenched with 1.5 N HCl solution until pH 3.0. The resulting reaction mixture was filtered through celite pad, layers were separated and the aqueous layer was re-extracted with ethyl acetate (2 x 2000 mL). The combined organic layers were

washed with water (800 mL), brine (500 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified on flash column chromatography (silica gel, 230-400 mesh) using 1% to 2% ethyl acetate in petroleum ether to provide (R)-pent-4-en-2-yl 4-methylbenzenesulfonate (207 g, 50% yield) as a colourless liquid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.83 – 7.75 (m, 2H), 7.37 – 7.31 (m, 2H), 5.69 – 5.52 (m, 1H), 5.09 – 5.04 (m, 1H), 5.01 (t, *J* = 1.3 Hz, 1H), 4.65 (h, *J* = 6.3 Hz, 1H), 2.45 (s, 3H), 2.37 – 2.22 (m, 2H), 1.26 (d, *J* = 6.3 Hz, 3H).

Step 2: (S)-N,N-bis(4-methoxybenzyl)-2-methylpent-4-ene-1-sulfonamide

To a stirred solution of N,N-bis(4-methoxybenzyl)methanesulfonamide (207 g, 617 mmol, 1.0 equiv) in THF (2000 mL) was added n-BuLi (321 mL, 802 mmol, 2.5 M in hexane) at -78 °C. The resulting reaction mixture was stirred for 1 h at same temperature followed by (R)-pent-4-en-2-yl 4-methylbenzenesulfonate (206 g, 858 mmol) in THF (400 mL) was added dropwise at -78 °C. The reaction mixture was allowed to warm to ambient temperature and stirred for 16 h. After the reaction was complete (monitored by TLC), the reaction mixture was quenched with saturated ammonium chloride solution, layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 2000 mL). The combined organic layers were washed with water (1000 mL), brine (600 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 230-400 mesh) using 2% to 4% ethyl acetate in petroleum ether to provide (S)-N,N-bis(4-methoxybenzyl)-2-methylpent-4-ene-1-sulfonamide (105 g, 42.2% yield) as a colourless liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.25 – 7.20 (m, 4H), 6.92 – 6.85 (m, 4H), 5.70 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 5.12 – 4.98 (m, 2H), 4.32 – 4.19 (m, 4H), 3.83 (s, 6H), 2.90 – 2.80 (m, 1H), 2.66 – 2.55 (m, 1H), 2.27 – 2.17 (m, 1H), 2.17 – 2.02 (m, 2H), 1.11 (d, *J* = 6.7, 3H).

Step 3: (2S,3S)-N,N-bis(4-methoxybenzyl)-3-methyl-1-phenylhex-5-ene-2-sulfonamide AND (2R,3S)-N,N-bis(4-methoxybenzyl)-3-methyl-1-phenylhex-5-ene-2-sulfonamide

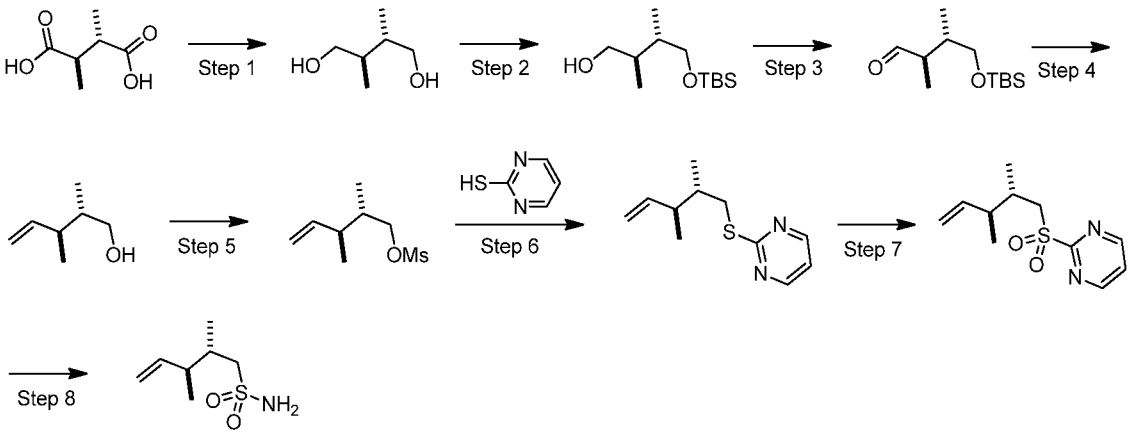
To a stirred solution of (S)-N,N-bis(4-methoxybenzyl)-2-methylpent-4-ene-1-sulfonamide (65 g, 161 mmol) in THF (650 mL) was added n-butyl lithium (140.9 mL, 226 mmol, 1.6 M in hexane) at -78 °C. The reaction mixture was stirred for 20 min at same temperature. (Bromomethyl)benzene (110 g, 644 mmol) was added dropwise at same temperature and stirred for 30 min at -78 °C. The resulting reaction mixture was warmed to ambient temperature and stirred for 1 h. After the reaction was complete (monitored by TLC), the reaction mixture was quenched with saturated ammonium chloride solution, layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 500 mL). The combined organic layers were washed with water (300 mL), brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 230-400 mesh) using 2% to 4% ethyl acetate in petroleum ether as an eluent to provide (2S,3S)-N,N-bis(4-methoxybenzyl)-3-methyl-1-phenylhex-5-ene-2-sulfonamide AND (2R,3S)-N,N-bis(4-methoxybenzyl)-3-methyl-1-phenylhex-5-ene-2-sulfonamide (60.5 g, 76% yield) as a colourless liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.28 – 7.14 (m, 7H), 7.02 – 6.92 (m, 2H), 6.90 – 6.84 (m, 4H), 5.60 – 5.52 (m, 1H), 5.04 – 4.82 (m, 2H), 4.54 – 4.32 (m, 2H), 4.10 – 3.96 (m, 2H), 3.84 – 3.80 (m, 6H), 3.28 – 3.12 (m, 2H), 2.98 – 2.88 (m, 1H), 2.42 – 2.08 (m, 1H), 2.00 – 1.76 (m, 2H), 1.18 – 1.04 (m, 3H).

Step 4: (2S,3S)-3-methyl-1-phenylhex-5-ene-2-sulfonamide AND (2R,3S)-3-methyl-1-phenylhex-5-ene-2-sulfonamide

To a stirred solution of (2S,3S)-N,N-bis(4-methoxybenzyl)-3-methyl-1-phenylhex-5-ene-2-sulfonamide AND (2R,3S)-N,N-bis(4-methoxybenzyl)-3-methyl-1-phenylhex-5-ene-2-sulfonamide (60 g, 122 mmol) in anisole (99 g, 915 mmol) was added TFA (148 g, 1298 mmol) at 0 °C. The resulting reaction

mixture was heated to 40 °C for 16 h. After the reaction was completed (monitored by TLC), volatiles were removed under reduced pressure and the crude was purified by flash column chromatography (silica gel, 230-400 mesh) using 15% to 20% ethyl acetate in petroleum ether as an eluent to provide (2S,3S)-3-methyl-1-phenylhex-5-ene-2-sulfonamide AND (2R,3S)-3-methyl-1-phenylhex-5-ene-2-sulfonamide (21.5 g, 70% yield) as liquid. MS (ESI, -ve ion) *m/z* 254.2 $(M-1)^-$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.37 – 7.15 (m, 5H), 6.94 – 6.86 (m, 2H), 5.62 – 5.54 (m, 1H), 4.96 – 4.70 (m, 2H), 3.32 – 3.20 (m, 2H), 2.92 – 2.80 (m, 1H), 2.49 – 2.28 (m, 1H), 2.10 – 1.78 (m, 2H), 1.08 – 0.90 (m, 3H).

(2S,3S)-2,3-Dimethylpent-4-ene-1-sulfonamide



Step 1: meso-2,3-dimethylbutane-1,4-diol

A solution of meso-2,3-dimethylsuccinic acid (50.0 g, 342 mmol) in THF (700 mL) was cooled to 0 °C. Lithium aluminum hydride (2.0 M solution in tetrahydrafuran, 428.0 mL, 855.0 mmol) was then cannulated into the addition funnel, and then added into the stirred cooled mixture dropwise over 15 min. After the addition was completed the reaction was allowed to warm to room temperature and stirred for 12 h under a nitrogen atmosphere. The reaction mixture was quenched with MeOH (350 mL) dropwise at 0 °C and then 20 % KOH (150 mL) aqueous solution was added slowly. The reaction mixture was stirred at 0 °C for

20 min, EtOAc (1000 mL) was added and the organic phase was dried over $MgSO_4$ filtered and concentrated under reduced pressure to give meso-2,3-dimethylbutane-1,4-diol (40.0 g, 100% yield) which was used as such in next step. MS (ESI, +ve ion) *m/z* 119.2 $(M+H)^+$.

Step 2: rac-(2R,3S)-4-((tert-butyldimethylsilyl)oxy)-2,3-dimethylbutan-1-ol

To a suspension of sodium hydride (60% dispersion in mineral oil, 20.31 g, 508.0 mmol) in THF (1200 mL) at 0 °C under a N_2 atmosphere was added a solution of meso-2,3-dimethylbutane-1,4-diol (40.0 g, 338.0 mmol) in THF (200 mL) dropwise over 20 min. After addition, the reaction was heated at 55 °C for 45 min and cooled to 0 °C. The reaction mixture was treated with a solution of tert-butyldimethylsilyl chloride (51.0 g, 338.0 mmol) in THF (200 mL). The reaction was stirred at room temperature for 12 h. The reaction was quenched by adding saturated NH_4Cl (500 mL) and diluted with EtOAc (500 mL). The separated aqueous layer was extracted with EtOAc (3 x 500 mL) and the combined organic extracts was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give rac-(2R,3S)-4-((tert-butyldimethylsilyl)oxy)-2,3-dimethylbutan-1-ol (70.0 g, 301.0 mmol, 89% yield) which was used as such in next step. MS (ESI, +ve ion) *m/z* 233.0 $(M+H)^+$.

Step 3: rac-(2R,3S)-4-((tert-butyldimethylsilyl)oxy)-2,3-dimethylbutanal

To a solution of rac-(2R,3S)-4-((tert-butyldimethylsilyl)oxy)-2,3-dimethylbutan-1-ol (70.0 g, 301.0 mmol) and (diacetoxyiodo)benzene (107.0 g, 301.0 mmol) in DCM (250 mL) was added 2,2,6,6-tetramethyl-1-piperidinyloxy (2.35 g, 15.06 mmol) in one portion at room temperature. The reaction mixture was stirred for 12 h at room temperature. The reaction mixture was poured into DCM (500 mL) and washed with saturated aqueous sodium bicarbonate solution (250 mL) and brine (250 mL). The organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. The crude material was purified by column chromatography using silica gel 60-120 mesh, eluting with 0% to 10% EtOAc in

hexane to give rac-(2R,3S)-4-((tert-butyldimethylsilyl)oxy)-2,3-dimethylbutanal (45.0 g, 195.0 mmol, 64.7% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.51 (dd, J = 10.1, 5.2 Hz, 1H), 3.40 (dd, J = 10.0, 8.2 Hz, 1H), 2.35 – 2.22 (m, 2H), 0.94 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 6.9 Hz, 3H), 0.83 (s, 9H). 0.03 (s, 3H) 0.01 (s, 3H). MS (ESI, +ve) *m/z* 231.2 $(M+H)^+$.

Step 4: rac-(2S,3S)-2,3-dimethylpent-4-en-1-ol

A solution of methyl triphenylphosphonium bromide (185.0 g, 521.0 mmol) in THF (1500 mL) was treated with n-butyllithium (2.5 M solution in hexane, 174.0 mL, 18.8 mmol) at 0 °C. After 10 min, the resulting yellow mixture was allowed to stir at room temperature for 20 min. A solution of rac-(2R,3S)-4-((tert-butyldimethylsilyl)oxy)-2,3-dimethylbutanal (40.0 g, 174.0 mmol) in THF (50 mL) was added to the reaction mixture at -78 °C. After 10 min, the reaction mixture was allowed to stirred at 0 °C for 2 h and then quenched with saturated aqueous NH_4Cl (500 mL) solution and water (200 mL). Diethylether (500 mL) was added and layers were separated. The aqueous layer was extracted with ether (3 x 500 mL). The combined organic layer was dried over $MgSO_4$, and concentrated under reduced pressure to get the crude material. The crude compound was dissolved in DCM (300 mL) and treated with 1.0 N HCl in diethylether (250 mL). The reaction mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure and the crude product was purified by column chromatography using silica gel (60-120 mesh), eluting with 0% to 30% EtOAc in hexane to give rac-(2S,3S)-2,3-dimethylpent-4-en-1-ol (8.0 g, 70.1 mmol, 40.2% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.82 – 5.61 (m, 1H), 5.04 – 4.87 (m, 2H), 4.37 (t, J = 5.2 Hz, 1H), 3.39 – 3.25 (m, 1H), 3.19 (ddd, J = 10.5, 6.7, 5.2 Hz, 1H), 2.33 – 2.16 (m, 1H), 1.56 – 1.36 (m, 1H), 0.95 (d, J = 6.9 Hz, 3H), 0.76 (d, J = 6.9 Hz, 3H). MS (ESI, +ve) *m/z* 115.1 $(M+H)^+$.

Step 5: rac-(2S,3S)-2,3-dimethylpent-4-en-1-yl methanesulfonate

To a solution of rac-(2S,3S)-2,3-dimethylpent-4-en-1-ol (5.0 g, 43.8 mmol) and triethylamine (13.43 mL, 96.0 mmol) in DCM (200 mL) was added methanesulfonyl chloride (5.12 mL, 65.7 mmol, 1.5 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. Then the reaction was quenched with saturated NH_4Cl (100 mL) solution and extracted with EtOAc (3 x 200 mL) and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give rac-(2S,3S)-2,3-dimethylpent-4-en-1-yl methanesulfonate which was used without further purification. MS (ESI, +ve) *m/z* 193.2 $(M+H)^+$.

Step 6: rac-2-(((2S,3S)-2,3-dimethylpent-4-en-1-yl)thio)pyrimidine

A solution of 2-mercapto-pyrimidine (27.5 g, 245.0 mmol) and potassium carbonate (36.3 g, 263.0 mmol) in DMF (1000 mL) was stirred at room temperature for 10 min. A solution of rac-(2S,3S)-2,3-dimethylpent-4-en-1-yl methanesulfonate (337 g, 175.0 mmol) in THF (1000 mL) was added at room temperature. The resulting mixture was heated to 50 °C for 4 h and stirred at room temperature for 12 h. The crude mixture was quenched with cold water (500 mL) and extracted with EtOAc (3 x 500 mL). The combined organic layer was concentrated under reduced pressure. The crude material was purified by column chromatography (EtOAc/hexanes, 0% to 15 %, silica gel) to give rac-2-(((2S,3S)-2,3-dimethylpent-4-en-1-yl)thio)pyrimidine (19.0 g, 91.0 mmol, 52% yield). ^1H NMR (300 MHz, Chloroform-d) δ 8.50 (d, J = 4.7 Hz, 2H), 6.94 (t, J = 4.8 Hz, 1H), 5.76 (ddd, J = 16.8, 10.6, 8.2 Hz, 1H), 5.19 – 4.97 (m, 2H), 3.25 (dd, J = 13.2, 5.9 Hz, 1H), 2.99 (dd, J = 13.1, 7.9 Hz, 1H), 2.50 – 2.32 (m, 1H), 1.93 – 1.74 (m, 1H), 1.07 (d, J = 6.8 Hz, 3H), 1.00 (d, J = 6.9 Hz, 3H). MS (ESI, +ve) *m/z* 209.0 $(M+H)^+$.

Step 7: rac-2-(((2S,3S)-2,3-dimethylpent-4-en-1-yl)sulfonyl)pyrimidine

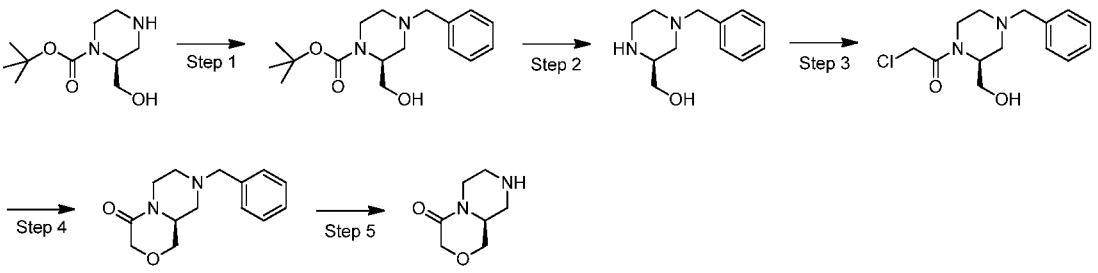
To a solution of rac-2-(((2S,3S)-2,3-dimethylpent-4-en-1-yl)thio)pyrimidine (25.0 g, 120.0 mmol) in acetonitrile (500 mL) and water (50 mL) was added soduim tungstate dehydrate (7.92 g, 24.0 mmol) followed by

hydrogen peroxide (61.3 mL, 600.0 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with saturated sodium thiosulfate (750 mL). The reaction mixture was extracted with ethyl-acetate (3 x 1000 mL) and combined organic layer was dried over sodium-sulphate, filtered and concentrated under reduced pressure to give rac-2-(((2S,3S)-2,3-dimethylpent-4-en-1-yl)sulfonyl)pyrimidine (25.0 g, 104.0 mmol, 86% yield). ^{1}H NMR (400 MHz, Chloroform-d) δ 8.98 (d, J = 4.8 Hz, 2H), 7.59 (t, J = 4.9 Hz, 1H), 5.78 – 5.59 (m, 1H), 5.14 – 5.01 (m, 2H), 3.58 (dd, J = 14.3, 4.0 Hz, 1H), 3.32 (dd, J = 14.3, 8.5 Hz, 1H), 2.48 – 2.28 (m, 2H), 1.10 (d, J = 6.8 Hz, 3H), 1.03 (d, J = 6.8 Hz, 3H). MS (ESI, +ve) *m/z* 241.2 $(M+H)^+$.

Step 8: rac-(2S,3S)-2,3-dimethylpent-4-ene-1-sulfonamide

To a solution of rac-2-(((2S,3S)-2,3-dimethylpent-4-en-1-yl)sulfonyl)pyrimidine (25.0 g, 104.0 mmol) in methanol (500 mL) was added sodium methoxide (22.48 g , 104.0 mmol). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure. The crude mixture was diluted with water (500 mL) and washed with ethyl acetate (3 x 250 mL). Sodium acetate (10.24 g, 125 mmol) and hydroxylamine-o-sulfonic acid (14.12 g, 125 mmol) was added to the aqueous layer. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was extracted with MTBE (3 x 500 mL) and the combined organic layer was washed with saturated sodium carbonate (2 x 300 mL), dried over sodium-sulphate, filtered and concentrated under reduced pressure to give rac-(2S,3S)-2,3-dimethylpent-4-ene-1-sulfonamide (14.0 g, 79.0 mmol, 76% yield). ^{1}H NMR (400 MHz, Chloroform-d) δ 5.71 (ddd, J = 17.8, 10.5, 7.2 Hz, 1H), 5.19 – 4.92 (m, 4H), 3.19 (dd, J = 14.6, 3.7 Hz, 1H), 2.89 (dd, J = 14.6, 8.3 Hz, 1H), 2.36 (q, J = 6.2 Hz, 1H), 2.19 (th, J = 7.5, 4.0, 3.3 Hz, 1H), 1.11 (dd, J = 6.6, 2.9 Hz, 3H), 1.03 (dd, J = 6.7, 2.9 Hz, 3H). MS (ESI, +ve) *m/z* 178.2 $(M+H)^+$.

(S)-Hexahydropyrazino[2,1-c][1,4]oxazin-4(3H)-one



Step 1: (S)-tert-butyl 4-benzyl-2-(hydroxymethyl)piperazine-1-carboxylate

To a solution of (S)-1-boc-2-(hydroxymethyl)piperazine (5.0 g, 23.12 mmol) in 1,2-dichloroethane (100 mL) was added benzaldehyde (7.04 mL, 69.4 mmol). The resulting mixture was then stirred at room temperature for 30 min, and then sodium triacetoxyborohydride (6.85 mL, 46.2 mmol) was added. The resulting mixture was then stirred at room temperature overnight. Then, the mixture was quenched with saturated $NaHCO_3$ (20 mL) and was stirred at room temperature for 10 min. The organic layer was collected and aqueous layer was extracted with EtOAc (1 x 30 mL). The combined organic extracts were then dried over $MgSO_4$ and concentrated in vacuo. Chromatographic purification of the residue (silica gel, 0% to 100% EtOAc/heptane) provided (S)-tert-butyl 4-benzyl-2-(hydroxymethyl)piperazine-1-carboxylate (5.86 g, 19.13 mmol, 83% yield) as an oil. MS (ESI, +ve ion) *m/z* 307.3 $(M+H)^+$.

Step 2: (S)-(4-benzylpiperazin-2-yl)methanol

To a solution of (S)-tert-butyl 4-benzyl-2-(hydroxymethyl)piperazine-1-carboxylate (5.86 g, 19.13 mmol) in DCM (30 mL) was added trifluoroacetic acid (11.37 mL, 153 mmol). After addition, the mixture was then stirred at room temperature for 2.5 h. Then, additional trifluoroacetic acid (7 mL) was added and the mixture was stirred at room temperature for an additional 1 h. Then, the mixture was concentrated in vacuo and H_2O (10 mL) was added. The mixture was then adjusted to pH=14 with NaOH (1 N). The mixture was then extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried over $MgSO_4$, concentrated, and dried in vacuo at 40 °C overnight provided (S)-(4-benzylpiperazin-2-yl)methanol as an oil that was used withour further purification.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ 7.26 – 7.38 (5H, m) 3.62 – 3.81 (2H, m) 3.54 (2H, d, *J*=4.11 Hz) 3.25 – 3.35 (2H, m) 3.02 – 3.14 (1H, m) 2.77 – 2.90 (2H, m) 2.41 (1H, td, *J*=11.88, 2.45 Hz) 2.18 – 2.30 (1H, m). MS (ESI, +ve ion) *m/z* 207.1 $(M+H)^+$.

Step 3: (S)-1-(4-benzyl-2-(hydroxymethyl)piperazin-1-yl)-2-chloroethanone

To a solution of (S)-(4-benzylpiperazin-2-yl)methanol (1.4 g, 6.79 mmol) and triethylamine (2.83 mL, 20.36 mmol) in DCM (5 mL) at 0 °C under N_2 was added chloroacetyl chloride (0.540 mL, 6.79 mmol) dropwise. After addition, the mixture was then stirred at 0 °C for 48 min. Then, MeOH (10 mL) was added and the mixture was concentrated in vacuo. Chromatographic purification of the residue (silica gel, 0% to 100% EtOAc/heptane) provided (S)-1-(4-benzyl-2-(hydroxymethyl)piperazin-1-yl)-2-chloroethanone (530 mg, 1.874 mmol, 27.6% yield) as an oil. MS (ESI, +ve ion) *m/z* 283.1 $(M+H)^+$.

Step 4 : (S)-8-benzylhexahydropyrazino[2,1-c][1,4]oxazin-4(3H)-one

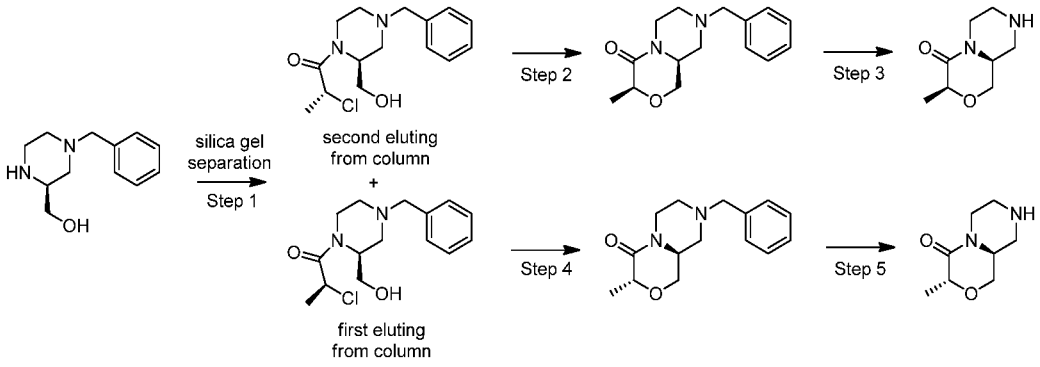
To a solution of (S)-1-(4-benzyl-2-(hydroxymethyl)piperazin-1-yl)-2-chloroethanone (530 mg, 1.874 mmol) in THF (40 mL) at 0 °C under N_2 was added potassium tert-butoxide (421 mg, 3.75 mmol). After addition, the mixture was stirred at 0 °C for 2 h. LCMS showed no starting material. Then, MeOH (10 mL) was added and the mixture was concentrated in vacuo. Chromatographic purification of the residue (silica gel, 0% to 100% EtOAc/heptane) provided (S)-8-benzylhexahydropyrazino[2,1-c][1,4]oxazin-4(3H)-one (262 mg, 1.064 mmol, 56.8% yield) as an oil. MS (ESI, +ve ion) *m/z* 247.1 $(M+H)^+$.

Step 4 : (S)-hexahydropyrazino[2,1-c][1,4]oxazin-4(3H)-one

A solution of (S)-8-benzylhexahydropyrazino[2,1-c][1,4]oxazin-4(3H)-one (262 mg, 1.064 mmol) and acetic acid (0.123 mL, 2.127 mmol) in methanol (2.5 mL) in a pressure vial was added a solution of palladium (5% on activated carbon, 34 mg, 0.319 mmol) in EtOAc (0.3 mL). Then, the mixture was degassed

with hydrogen 5 times, and then was charged with hydrogen at 40 psi. The mixture was then stirred for 3.5 h. LCMS showed some starting material. Then, palladium (5% on activated wood carbon, 34 mg, 0.319 mmol) and acetic acid (0.123 mL, 2.127 mmol) were added. Then, the mixture was degassed 5 times with hydrogen, and then charged with hydrogen at 40 psi. The resulting mixture was stirred at room temperature overnight at 40 psi. Then, the mixture was filtered through celite and the celite was washed with MeOH/EtOAc 1:1 (2 x 3 mL). The combined filtrates were concentrated and dried in vacuo provided (S)-hexahydropyrazino[2,1-c][1,4]oxazin-4(3H)-one (166 mg, 1.063 mmol, 100% yield) as an oil, which was used without further purification. MS (ESI, +ve ion) *m/z* 157.1$(M+H)^+$.

(3S,9aS)-3-methylhexahydropyrazino[2,1-c][1,4]oxazin-4(3H)-one AND (3R,9aS)-3-methylhexahydropyrazino[2,1-c][1,4]oxazin-4(3H)-one



Step 1: (S)-1-((S)-4-benzyl-2-(hydroxymethyl)piperazin-1-yl)-2-chloropropan-1-one AND (R)-1-((S)-4-benzyl-2-(hydroxymethyl)piperazin-1-yl)-2-chloropropan-1-one

To a solution of (S)-(4-benzylpiperazin-2-yl)methanol (1.4 g, 6.79 mmol) and triethylamine (2.83 mL, 20.36 mmol) in DCM (10 mL) at 0 °C was added 2-chloropropionyl chloride (0.862 mL, 6.79 mmol). After addition, the mixture was stirred at 0 °C for 2 h. LCMS showed no starting material. Then, MeOH (10 mL) was added and the mixture was concentrated in vacuo. Chromatographic purification of the residue (silica gel, 0% to 100% EtOAc/heptane) provided (S)-

1-((S)-4-benzyl-2-(hydroxymethyl)piperazin-1-yl)-2-chloropropan-1-one (176 mg, 0.593 mmol, 8.74% yield) as an oil and the first eluting isomer from the silica gel column. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ 7.28 – 7.40 (5H, m) 4.46 – 4.73 (2H, m) 4.14 (1H, br s) 3.69 – 4.03 (3H, m) 3.41 – 3.63 (2H, m) 3.10 (1H, br s) 2.93 (1H, br s) 2.35 (1H, br s) 2.02 – 2.23 (1H, m) 1.65 – 1.69 (3H, m). MS (ESI, +ve ion) *m/z* 297.0 $(M+H)^+$. In addition, (R)-1-((S)-4-benzyl-2-(hydroxymethyl)piperazin-1-yl)-2-chloropropan-1-one (142 mg, 0.478 mmol, 7.1% yield) was isolated as an oil and the second eluting isomer from the silica gel column. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ 7.27 – 7.40 (5H, m), 4.60 – 4.72 (1H, m), 4.44 – 4.59 (1H, m), 3.97 (1H, d, *J*=4.30 Hz), 3.68 – 3.93 (3H, m), 3.51 (2H, d, *J*=18.58 Hz), 3.07 (1H, br s), 2.92 (1 H, br s), 2.11 – 2.45 (2H, m), 1.64 – 1.73 (3H, m). MS (ESI, +ve ion) *m/z* 297.0 $(M+H)^+$.

Step 2 : (3S,9aS)-8-benzyl-3-methylhexahydropyrazino[2,1-c][1,4]oxazin-4(3H)-one

To a solution of (R)-1-((S)-4-benzyl-2-(hydroxymethyl)piperazin-1-yl)-2-chloropropan-1-one (142 mg, 0.478 mmol) in THF (50 mL) under nitrogen at 0 °C was added potassium tert-butoxide (59.1 mg, 0.526 mmol). The resulting mixture was then stirred at 0 °C for 1 h and at room temperature for 10 d. Then, MeOH (10 mL) was added and the mixture was concentrated in vacuo. Chromatographic purification of the residue (silica gel, 0% to 100% EtOAc/heptane) provided (3S,9aS)-8-benzyl-3-methylhexahydropyrazino[2,1-c][1,4]oxazin-4(3H)-one (33 mg, 0.127 mmol, 26.5% yield) as an oil. ^{1}H NMR (400 MHz, DICHLOROMETHANE-d_2) δ 7.11 – 7.28 (6H, m), 4.31 – 4.42 (1H, m), 4.02 – 4.10 (1H, m), 3.69 – 3.77 (1H, m), 3.54 – 3.63 (1H, m), 3.37 – 3.49 (3H, m), 2.63 – 2.80 (3H, m), 1.92 – 2.05 (2H, m), 1.31 (3H, d, J=6.85 Hz). MS (ESI, +ve ion) *m/z* 261.1$(M+H)^+$.

Step 3 : (3S,9aS)-3-methylhexahydropyrazino[2,1-c][1,4]oxazin-4(3H)-one

To a solution of (3S,9aS)-8-benzyl-3-methylhexahydropyrazino[2,1-c][1,4]oxazin-4(3H)-one (33 mg, 0.127 mmol) in methanol (0.5 mL) was added

acetic acid (0.015 mL, 0.254 mmol) and palladium (10 wt% dry basis on activated carbon, wet, degussa type, 6.74 mg, 0.063 mmol). The resulting mixture was then purged with hydrogen, then was charged with hydrogen at 40 psi. The resulting mixture was then stirred at room temperature overnight. Then, the mixture was filtered through celite and the celite was washed with EtOAc (2 x 3 mL). The combined filtrates were concentrated in vacuo and chromatographic purification of the residue (silica gel, 0% to 50% MeOH/DCM) provided (3S,9aS)-3-methylhexahydropyrazino[2,1-c][1,4]oxazin-4(3H)-one (20 mg, 0.118 mmol, 93% yield) as an oil. ^{1}H NMR (400 MHz, DICHLOROMETHANE-d_2) δ 4.43 – 4.58 (1H, m), 4.09 – 4.19 (1H, m), 3.86 (1H, dd, J=12.52, 4.50 Hz), 3.66 – 3.75 (1H, m), 3.53 (1H, td, J=7.53, 3.72 Hz), 2.97 – 3.12 (2H, m), 2.65 – 2.87 (3H, m), 1.41 (3H, d, J=6.85 Hz). MS (ESI, +ve ion) *m/z* 171.1$(M+H)^+$.

Step 4: (3R,9aS)-8-benzyl-3-methylhexahydropyrazino[2,1-c][1,4]oxazin-4(3H)-one

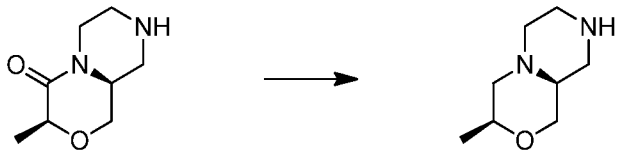
To a solution of (S)-1-((S)-4-benzyl-2-(hydroxymethyl)piperazin-1-yl)-2-chloropropan-1-one (176 mg, 0.593 mmol) in THF (50 mL) at 0 °C under nitrogen was added potassium tert-butoxide (100 mg, 0.890 mmol). After addition, the mixture was then stirred at 0 °C for 30 min. LCMS showed no starting material. Then, saturated $NaHCO_3$ (5 mL) was added and the mixture was extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried over $MgSO_4$, concentrated, and dried in vacuo provided (3R,9aS)-8-benzyl-3-methylhexahydropyrazino[2,1-c][1,4]oxazin-4(3H)-one (154 mg, 0.592 mmol, 100% yield) as an oil, which was used without purification. MS (ESI, +ve ion) *m/z* 261.0 $(M+H)^+$.

Step 5: (3R,9aS)-3-methylhexahydropyrazino[2,1-c][1,4]oxazin-4(3H)-one

To a solution of (3R,9aS)-8-benzyl-3-methylhexahydropyrazino[2,1-c][1,4]oxazin-4(3H)-one (154 mg, 0.592 mmol) in methanol (2 mL) was added a solution of palladium (10 wt% dry basis on activated carbon, wet, degussa type, 18.89 mg, 0.177 mmol) in EtOAc (0.2 mL). The resulting mixture was then

purged with hydrogen five times and charged with hydrogen at 40 psi. The resulting mixture was then stirred for 10 d. Then, the mixture was filtered through celite and the celite was washed with EtOAc (2 x 5 mL). The combined filtrates were concentrated. Chromatographic purification of the residue (silica gel, 0% to 20% MeOH/DCM) provided (3R,9aS)-3-methylhexahydropyrazino[2,1-c][1,4]oxazin-4(3H)-one (93 mg, 0.546 mmol, 92% yield) as an oil. ^{1}H NMR (400 MHz, DICHLOROMETHANE-d_2) δ ppm 4.27 – 4.45 (1H, m), 4.05 (1H, q, J=6.85 Hz), 3.74 (1H, dd, J=12.23, 4.60 Hz), 3.54 – 3.63 (1H, m), 3.24 – 3.36 (1H, m), 2.84 – 2.91 (1H, m), 2.80 (1H, dd, J=11.74, 2.74 Hz), 2.50 – 2.67 (3H, m), 1.32 (3H, d, J=6.85 Hz). MS (ESI, +ve ion) *m/z* 171.1 $(M+H)^+$.

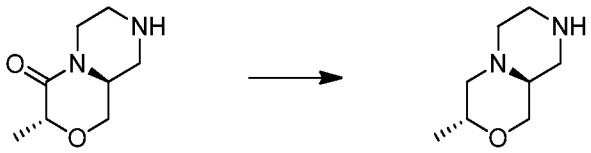
(3S,9aS)-3-Methyloctahydropyrazino[2,1-c][1,4]oxazine



To a solution of (3S,9aS)-3-methylhexahydropyrazino[2,1-c][1,4]oxazin-4(3H)-one (52 mg, 0.306 mmol) in 1,4-dioxane (4 mL) at room temperature under nitrogen was added lithium aluminium hydride (2.0 M in THF, 1.22 mL, 2.44 mmol) dropwise. After addition, the mixture was then stirred at 80 °C for 6 h. Then, the mixture was quenched with 2-propanol (1 mL) at 0 °C followed by saturated Na_2SO_4 (3 mL). The mixture was then stirred at room temperature for 30 min and then was filtered. The filtered cake was washed with MeOH (2 x 5 mL). The combined filtrates were concentrated and dried in vacuo. The residue was then dissolved in MeOH (5 mL) and silica gel was added. The mixture was concentrated and dried in vacuo. The solid mixture was then purified by silica gel column chromatography using ISCO instrument (solid loading, 0% to 20% ammonia in MeOH 2 M/DCM) provided (3S,9aS)-3-methyloctahydropyrazino[2,1-c][1,4]oxazine (67 mg, 0.429 mmol, 140% yield) as a solid that contained residual solvent and was used withour further purification.

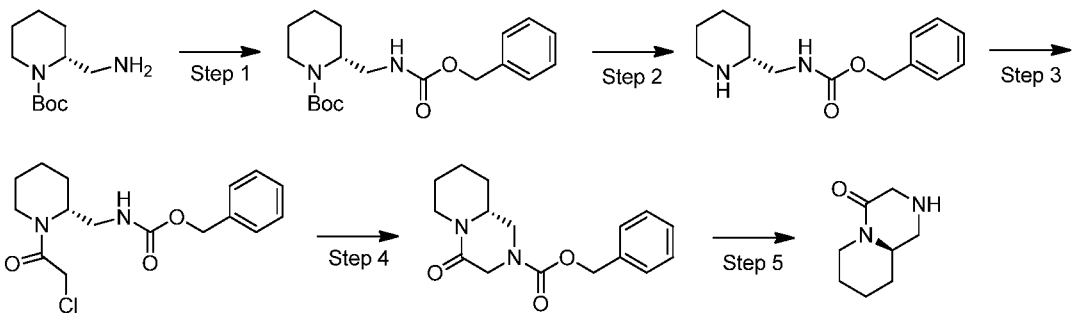
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ 3.94 (1H, dt, *J*=6.55, 3.37 Hz), 3.72 (1H, q, *J*=7.04 Hz), 3.52 – 3.59 (2H, m), 3.03 – 3.10 (2H, m), 2.86 – 2.96 (1H, m), 2.68 – 2.82 (5H, m), 1.90 (1H, br s), 1.34 (3H, d, *J*=6.65 Hz). MS (ESI, +ve ion) *m/z* 157.1 $(M+H)^+$.

(3R,9aS)-3-Methyloctahydropyrazino[2,1-c][1,4]oxazine



To a solution of (3R,9aS)-3-methylhexahydropyrazino[2,1-c][1,4]oxazin-4(3H)-one (80 mg, 0.470 mmol) in 1,4-dioxane (5 mL) under N_2 at room temperature was added lithium aluminium hydride (1.0 M in THF, 1.88 mL, 1.88 mmol) dropwise. After addition, the mixture was stirred at 80 °C for 6 h. Then, the mixture was quenched 2-propanol (1 mL) at 0 °C followed by saturated Na_2SO_4 (3 mL). The mixture was then stirred at room temperature for 30 min and then was filtered. The filtered cake was washed with MeOH (2 x 5 mL). The combined filtrates were concentrated and dried in vacuo. The residue was then dissolved in MeOH (5 mL) and silica gel was added. The mixture was concentrated and dried in vacuo. The solid mixture was then purified by silica gel column chromatography using ISCO instrument (solid loading, 0% to 20% ammonia in MeOH 2 M/DCM) provided (3R,9aS)-3-methyloctahydropyrazino[2,1-c][1,4]oxazine (20 mg, 0.128 mmol, 27.2% yield) as an oil. ^{1}H NMR (400 MHz, DICHLOROMETHANE-d_2) δ 3.92 (1H, ddd, *J*=6.50, 3.96, 2.25 Hz), 3.42 – 3.50 (1H, m), 3.30 – 3.37 (1H, m), 2.79 – 2.92 (2H, m), 2.53 – 2.68 (2H, m), 2.37 – 2.50 (3H, m), 2.06 – 2.24 (2H, m), 1.90 (1H, br s), 1.33 (3H, d, *J*=6.65 Hz). MS (ESI, +ve ion) *m/z* 157.2 $(M+H)^+$.

(R)-Hexahydro-1H-pyrido[1,2-a]pyrazin-4(6H)-one



Step 1: (R)-tert-butyl 2-((((benzyloxy)carbonyl)amino)methyl)piperidine-1-carboxylate

To a solution of (R)-tert-butyl 2-(aminomethyl)piperidine-1-carboxylate (475 mg, 2.216 mmol) in DCM (5.0 mL) at 0 °C was added *i*Pr$_2$Net (0.424 mL, 2.438 mmol) followed by benzyl chloroformate (0.693 mL, 2.438 mmol). The resulting mixture was then stirred at 0 °C for 2 h and at room temperature for 14 h. Then, saturated $NaHCO_3$ (30 mL) was added to the mixture and the mixture was stirred at room temperature for 3 min. The organic layer was collected and aqueous layer was extracted with EtOAc (1 x 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Chromatographic purification of the residue (silica gel, 0% to 100% EtOAc/heptane) provided (R)-tert-butyl 2-((((benzyloxy)carbonyl)amino)methyl)piperidine-1-carboxylate (772 mg, 2.216 mmol, 100% yield) as an oil. MS (ESI, +ve ion) *m/z* 371.1 $(M+Na)^+$.

Step 2: (R)-benzyl (piperidin-2-ylmethyl)carbamate

A solution of (R)-tert-butyl 2-((((benzyloxy)carbonyl)amino)methyl)piperidine-1-carboxylate (772 mg, 2.216 mmol) in DCM (5 mL) was added trifluoroacetic acid (1.646 mL, 22.16 mmol). The resulting mixture was then stirred at room temperature for 2 h. Then, *i*Pr$_2$Net (3.85 mL, 22.16 mmol) was added dropwise to the mixture at 0 °C and the mixture was stirred at room temperature for 5 min. Then, the mixture was concentrated in vacuo and chromatographic purification of the residue (silica gel, 0% to 100% EtOH:EtOAc (3:1)/heptane) provided (R)-benzyl (piperidin-2-

ylmethyl)carbamate (495 mg, 90% yield) as an oil. MS (ESI, +ve ion) *m/z* 249.2 $(M+H)^+$.

Step 3: (R)-benzyl ((1-(2-chloroacetyl)piperidin-2-yl)methyl)carbamate

To a solution of (R)-benzyl (piperidin-2-ylmethyl)carbamate (150 mg, 0.604 mmol) in 1,2-dichloroethane (1 mL) and DCM (1 mL) at 0 °C under nitrogen was added *i*Pr$_2$Net (0.168 mL, 0.966 mmol) followed by chloroacetyl chloride (0.063 mL, 0.785 mmol). After addition, the mixture was then stirred at 0 °C for 1 h. Then, the mixture was quenched with saturated $NaHCO_3$ (2.5 mL) and extracted with EtOAc (2 x 3 mL). The combined organic extracts were then dried over Na_2SO_4 and concentrated in vacuo. Chromatographic purification of the residue (silica gel, 0% to 100% EtOAc/heptane) provided (R)-benzyl ((1-(2-chloroacetyl)piperidin-2-yl)methyl)carbamate (126 mg, 0.388 mmol, 64.2% yield) as a solid. MS (ESI, +ve ion) *m/z* 325.1 $(M+H)^+$.

Step 4: (R)-benzyl 4-oxohexahydro-1H-pyrido[1,2-a]pyrazine-2(6H)-carboxylate

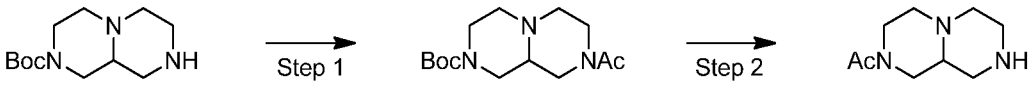
To a solution of (R)-benzyl ((1-(2-chloroacetyl)piperidin-2-yl)methyl)carbamate (126 mg, 0.388 mmol) in tetrahydrofuran (5 mL) was added sodium hydride (60% dispersion in mineral oil, 31 mg, 0.776 mmol) in portions. After addition, the mixture was then stirred at room temperature for 5 h. Then, the mixture was carefully quenched with water (5 mL). The mixture was then extracted with EtOAc (2 x 10 mL). The combined organic extracts were then dried over Na_2SO_4 and concentrated in vacuo. Chromatographic purification of the residue (silica gel, 0% to 100% EtOAc/heptane) provided (R)-benzyl 4-oxohexahydro-1H-pyrido[1,2-a]pyrazine-2(6H)-carboxylate (112 mg, 0.388 mmol, 100% yield) as an oil. MS (ESI, +ve ion) *m/z* 289.1 $(M+H)^+$.

Step 5: (R)-hexahydro-1H-pyrido[1,2-a]pyrazin-4(6H)-one

To a solution of (R)-benzyl 4-oxohexahydro-1H-pyrido[1,2-a]pyrazine-2(6H)-carboxylate (112 mg, 0.388 mmol) in ethanol (3 mL) was added

ammonium formate (122 mg, 1.942 mmol) and 10% palladium on carbon (124 mg, 0.117 mmol). The resulting mixture was then stirred at 70 °C for 1 h. The mixture was filtered through celite and the filter cake was washed with a mixture of EtOAc and MeOH (1:1, 3 x 2 mL). The combined filtrates were concentrated and chromatographic purification of the residue (silica gel, 0% to 15% 2 M ammonia in MeOH/DCM) provided (R)-hexahydro-1H-pyrido[1,2-a]pyrazin-4(6H)-one (54 mg, 0.350 mmol, 90% yield) as an oil. MS (ESI, +ve ion) *m/z* 155.1 $(M+H)^+$.

1-(Dihydro-1H-pyrazino[1,2-a]pyrazin-2(6H,7H,8H,9H,9aH)-yl)ethanone



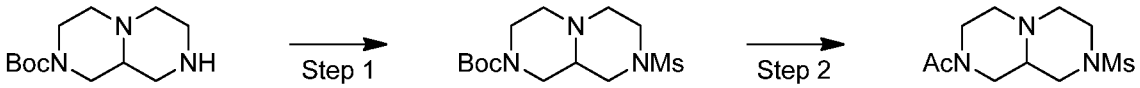
Step 1: tert-butyl 8-acetylhexahydro-1H-pyrazino[1,2-a]pyrazine-2(6H)-carboxylate

To stirred solution of tert-butyl hexahydro-1H-pyrazino[1,2-a]pyrazine-2(6H)-carboxylate (0.680 g, 2.82 mmol) in DCM (10 mL) was added at room temperature under argon diisopropylethylamine (1.078 mL, 6.20 mmol) followed by 2,5-dioxopyrrolidin-1-yl acetate (0.885 g, 5.64 mmol) in one portion as a solid. The resulting mixture was stirred at room temperature for 24 h. The crude mixture was directly loaded onto a silica gel precolumn (25 g), previously covered with a layer of sodium bicarbonate, and subjected to flash column chromatography on a 24 g ISCO gold column eluting with 0% to 3% MeOH/DCM to give tert-butyl 8-acetylhexahydro-1H-pyrazino[1,2-a]pyrazine-2(6H)-carboxylate as an oil. This was taken onto the next step without further purification. MS (ESI, +ve ion) *m/z* 306.4 $(M+Na)^+$.

Step 2: 1-(dihydro-1H-pyrazino[1,2-a]pyrazin-2(6H,7H,8H,9H,9aH)-yl)ethanone

To a solution of tert-butyl 8-acetylhexahydro-1H-pyrazino[1,2-a]pyrazine-2(6H)-carboxylate in DCM (10 mL) was added 2,2,2-trifluoroacetic acid (2.0 mL) at room temperature. The resulting mixture was stirred at room temperature overnight and the volatiles were removed to give 1-(hexahydro-1H-pyrazino[1,2-a]pyrazin-2(6H)-yl)ethanone 2,2,2-trifluoroacetate asa solid which was used without further purification.

2-(Methylsulfonyl)octahydro-1H-pyrazino[1,2-a]pyrazine



Step 1: tert-butyl 8-(methylsulfonyl)hexahydro-1H-pyrazino[1,2-a]pyrazine-2(6H)-carboxylate

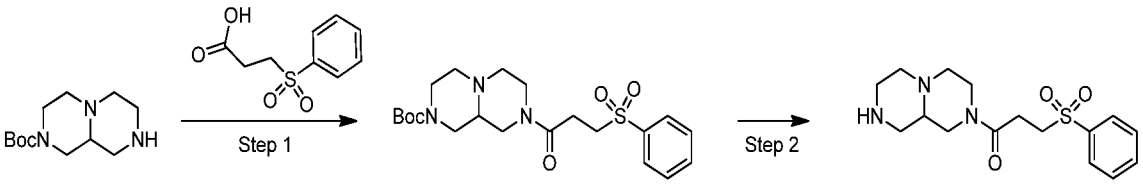
To a stirred ice-cooled mixture of tert-butyl hexahydro-1H-pyrazino[1,2-a]pyrazine-2(6H)-carboxylate (1.000 g, 4.14 mmol) and diisopropylethylamine (1.442 mL, 8.29 mmol) in DCM (14 mL) was dropwise added methanesulfonyl chloride (0.385 mL, 4.97 mmol) via a syringe. The resulting mixture was stirred at 0 °C for 10 min and stirred at ambient temperature for 19 h. The volatiles were removed and the residue was loaded onto a silica gel precolumn (25 g) and subjected to combi-flash column chromatography on a 24 g ISCO gold column eluting with 0% to 100% MeOH/DCM to give tert-butyl 8-(methylsulfonyl)hexahydro-1H-pyrazino[1,2-a]pyrazine-2(6H)-carboxylate (1.30 g, 4.07 mmol, 98% yield) as an oil. MS (ESI, +ve ion) *m/z* 320.1 $(M+1)^+$.

Step 2: 2-(methylsulfonyl)octahydro-1H-pyrazino[1,2-a]pyrazine

To a stirred solution of tert-butyl 8-(methylsulfonyl)hexahydro-1H-pyrazino[1,2-a]pyrazine-2(6H)-carboxylate (1.30 g, 4.07 mmol) in DCM (20 mL) was added 2,2,2-trifluoroacetic acid (2.0 mL, 4.14 mmol) via a syringe. The resulting mixture was stirred at room temperature for 2.5 h. Additional TFA (2 X 2.5 mL) was added over the first 2 h. The volatiles were removed in vacuo and the residue was subjected to high vacuum overnight to give 2.4 g of 2-

(methylsulfonyl)octahydro-1H-pyrazino[1,2-a]pyrazine 2,2,2-trifluoroacetate as a solid which was used without further purification. MS (ESI, +ve ion) *m/z* 220.2 $(M+1)^+$.

1-(Dihydro-1H-pyrazino[1,2-a]pyrazin-2(6H,7H,8H,9H,9aH)-yl)-3-(phenylsulfonyl)propan-1-one



Step 1: tert-butyl 8-(3-(phenylsulfonyl)propanoyl)hexahydro-1H-pyrazino[1,2-a]pyrazine-2(6H)-carboxylate

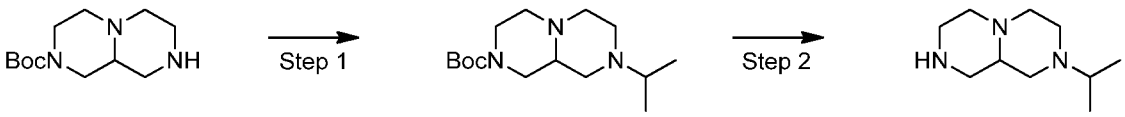
To a stirred mixture of tert-butyl hexahydro-1H-pyrazino[1,2-a]pyrazine-2(6H)-carboxylate (0.46 g, 1.906 mmol) and 3-(phenylsulfonyl)propionic acid (0.490 g, 2.287 mmol) in DCM (6.5 mL) was added at room temperature *i*Pr$_2$Net (0.829 mL, 4.77 mmol) via a syringe followed by HATU (1.450 g, 3.81 mmol) in one portion as a solid. The resulting mixture was stirred at room temperature for 75 min. The crude mixture was directly loaded onto a silica gel precolumn (25 g) and subjected to combi-flash column chromatography on a 24-g ISCO gold column eluting with 0% to 15% MeOH/DCM to give 1.28 g tert-butyl 8-(3-(phenylsulfonyl)propanoyl)hexahydro-1H-pyrazino[1,2-a]pyrazine-2(6H)-carboxylate as an oil which was taken onto the next step without further purification. MS (ESI, +ve ion) *m/z* 438.2 $(M+1)^+$.

Step 2: 1-(dihydro-1H-pyrazino[1,2-a]pyrazin-2(6H,7H,8H,9H,9aH)-yl)-3-(phenylsulfonyl)propan-1-one

A mixture of tert-butyl 8-(3-(phenylsulfonyl)propanoyl)hexahydro-1H-pyrazino[1,2-a]pyrazine-2(6H)-carboxylate (1.28 g, 2.93 mmol) and 2,2,2-trifluoroacetic acid (4.0 mL, 2.93 mmol) in DCM (15 mL) was stirred at room temperature for 50 min. The volatiles were removed and the residue was subjected

to high vacuum overnight to give 1.5 g of 1-(dihydro-1H-pyrazino[1,2-a]pyrazin-2(6H,7H,8H,9H,9aH)-yl)-3-(phenylsulfonyl)propan-1-one as an oil that was used without further purification. MS (ESI, +ve ion) *m/z* 338.1 $(M+1)^+$.

2-Isopropyloctahydro-1H-pyrazino[1,2-a]pyrazine



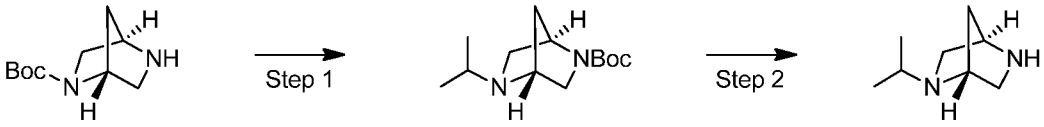
Step 1: tert-butyl 8-isopropylhexahydro-1H-pyrazino[1,2-a]pyrazine-2(6H)-carboxylate

A mixture of tert-butyl hexahydro-1H-pyrazino[1,2-a]pyrazine-2(6H)-carboxylate (0.53 g, 2.196 mmol) and acetone (0.806 mL, 10.98 mmol) in DCM (5.0 mL) was stirred at rt for 10 min before sodium triacetoxyhydroborate (2.327 g, 10.98 mmol) was added at room temperature in one portion as a solid. The resulting mixture was stirred at room temperature for 24 h. The reaction was quenched with MeOH (5 mL) and the resulting slurry was directly loaded onto a silica gel precolumn (25 g) and subjected to combi-flash column chromatography on a 12 g ISCO gold column eluting with 0% to 20% MeOH/DCM to give tert-butyl 8-isopropylhexahydro-1H-pyrazino[1,2-a]pyrazine-2(6H)-carboxylate (0.65 g, 2.293 mmol, 104% yield) as an oil. MS (ESI, +ve ion) *m/z* 284.3 $(M+1)^+$.

Step 2: 2-isopropyloctahydro-1H-pyrazino[1,2-a]pyrazine

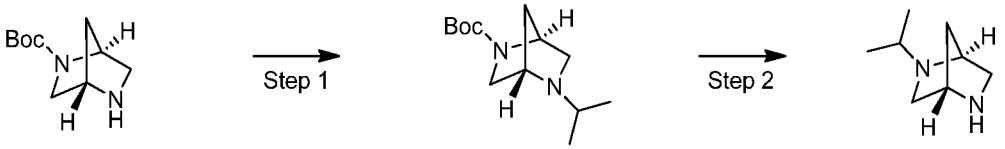
A mixture of tert-butyl 8-isopropylhexahydro-1H-pyrazino[1,2-a]pyrazine-2(6H)-carboxylate (0.65 g, 2.293 mmol) and 2,2,2-trifluoroacetic acid (4.0 mL, 2.293 mmol) in DCM (15 mL) was stirred at room temperature for 2 h. The volatiles were removed in vacuo and the residue was subjected to high vacuum overnight to give 1.74 g of 2-isopropyloctahydro-1H-pyrazino[1,2-a]pyrazine as an oil that was used without further purification. MS (ESI, +ve ion) *m/z* 184.2 $(M+1)^+$.

(1R,4R)-2-Isopropyl-2,5-diazabicyclo[2.2.1]heptane



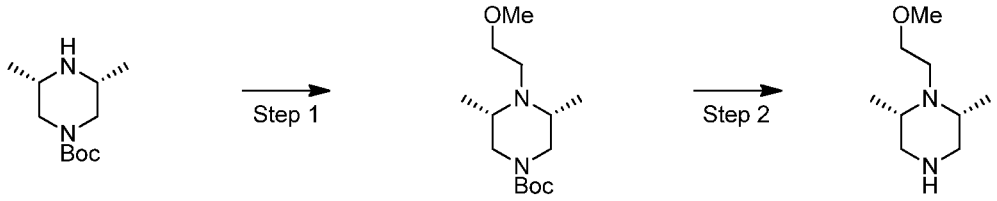
The title compound was synthesized, from (1R,4R)-tert-butyl 2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (AstaTech, Inc.), similarly using the protocol in the synthesis of 2-isopropyloctahydro-1H-pyrazino[1,2-a]pyrazine. MS (ESI, +ve ion) *m/z* 141.2 $(M+1)^+$.

(1S,4S)-2-Isopropyl-2,5-diazabicyclo[2.2.1]heptane



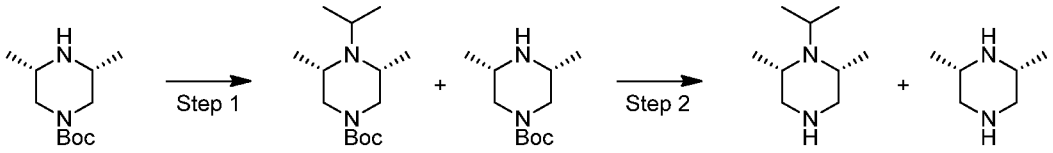
The title compound was synthesized, from (1S,4S)-tert-butyl 2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (AstaTech, Inc.), similarly using the protocol in the synthesis of 2-isopropyloctahydro-1H-pyrazino[1,2-a]pyrazine. MS (ESI, +ve ion) *m/z* 141.2 $(M+1)^+$.

Cis-1-(2-methoxyethyl)-2,6-dimethylpiperazine



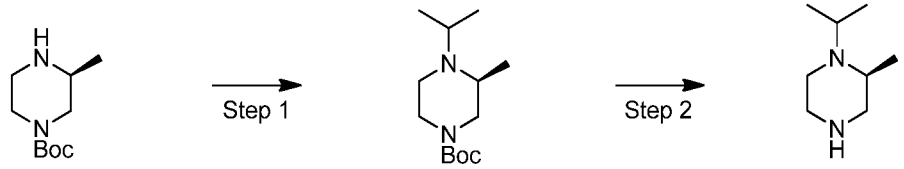
The title compound was synthesized, from cis-tert-butyl 3,5-dimethylpiperazine-1-carboxylate (AK Scientific), similarly using the protocol in the synthesis of 2-isopropyloctahydro-1H-pyrazino[1,2-a]pyrazine. MS (ESI, +ve ion) *m/z* 173.2 $(M+1)^+$.

Cis-1-isopropyl-2,6-dimethylpiperazine and cis-2,6-dimethylpiperazine



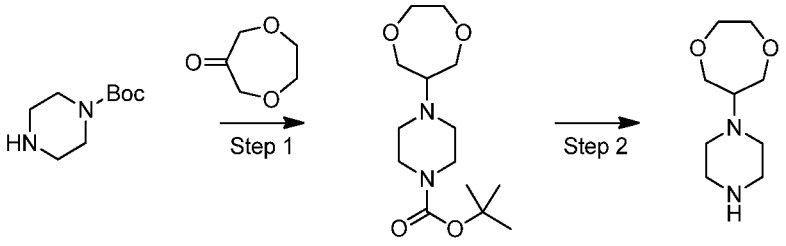
The title compounds were synthesized and used as a mixture, from cis-tert-butyl 3,5-dimethylpiperazine-1-carboxylate (AK Scientific), similarly using the protocol in the synthesis of 2-isopropyloctahydro-1H-pyrazino[1,2-a]pyrazine. MS (ESI, +ve ion) *m/z* 157.1 and 115.3 $(M+1)^+$.

(S)-1-Isopropyl-2-methylpiperazine



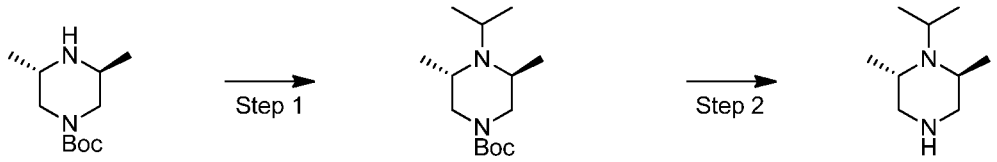
The title compound was synthesized, from (S)-tert-butyl 3-methylpiperazine-1-carboxylate, similarly using the protocol in the synthesis of 2-isopropyloctahydro-1H-pyrazino[1,2-a]pyrazine. MS (ESI, +ve ion) *m/z* 143.2 $(M+1)^+$.

1-(1,4-Dioxepan-6-yl)piperazine



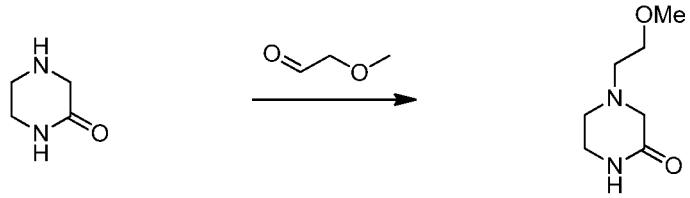
The title compound was synthesized, from 1,4-dioxepan-6-one (Enamine), similarly using the protocol in the synthesis of 2-isopropyloctahydro-1H-pyrazino[1,2-a]pyrazine. MS (ESI, +ve ion) *m/z* 187.2 $(M+1)^+$.

(2S,6S)-1-Isopropyl-2,6-dimethylpiperazine



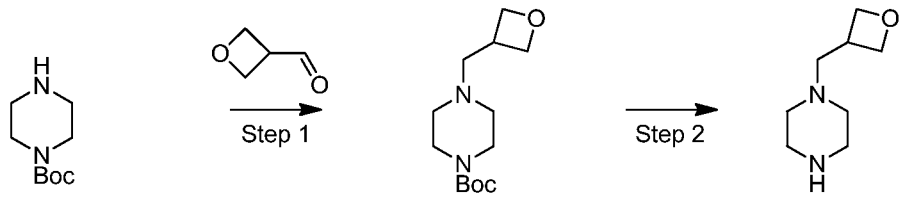
The title compound was synthesized, from (3S,5S)-tert-butyl 3,5-dimethylpiperazine-1-carboxylate (Anichem), similarly using the protocol in the synthesis of 2-isopropyloctahydro-1H-pyrazino[1,2-a]pyrazine. MS (ESI, +ve ion) *m/z* 157.2 $(M+1)^+$.

4-(2-Methoxyethyl)piperazin-2-one



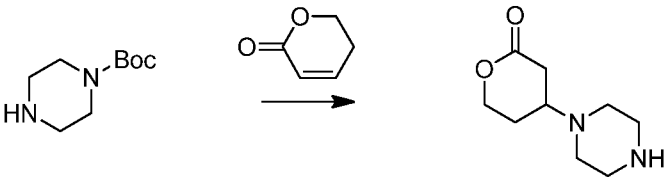
The title compound was synthesized, from piperazin-2-one (AK Scientific), similarly using the protocol in the synthesis (Step 1) of 2-isopropyloctahydro-1H-pyrazino[1,2-a]pyrazine.

1-(Oxetan-3-ylmethyl)piperazine



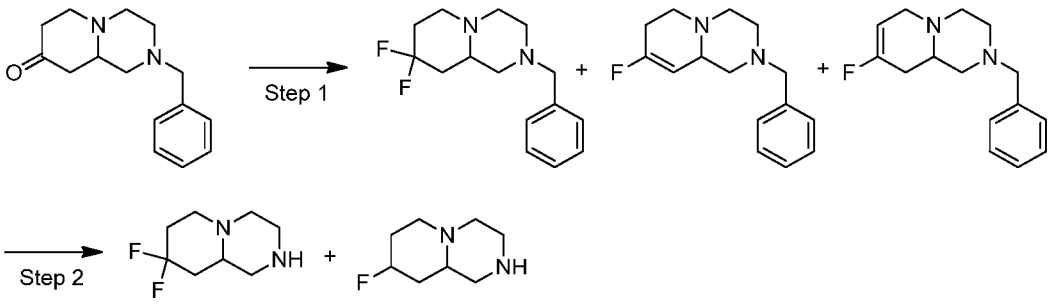
The title compound was synthesized, from tert-butyl piperazine-1-carboxylate, similarly using the protocol in the synthesis of 2-isopropyloctahydro-1H-pyrazino[1,2-a]pyrazine. MS (ESI, +ve ion) *m/z* 157.1 $(M+1)^+$.

4-(Piperazin-1-yl)tetrahydro-2H-pyran-2-one



To a stirred solution of 5,6-dihydro-2h-pyran-2-one (0.228 mL, 2.65 mmol) in DCM (1.0 mL) was added under argon a solution of piperazine-1-carboxylic acid tert-butyl ester (469 mg, 2.52 mmol) in DCM (2.0 mL). The resulting mixture was stirred at room temperature for a period of 3 d before trifluoroacetic acid (2.5 mL, 33.7 mmol) was added dropwise via a syringe. The resulting mixture was stirred at room temperature for a period of 2 h. The mixture was concentrated in vacuo and the residue was dried to give impure 4-(piperazin-1-yl)tetrahydro-2H-pyran-2-one. This was used without further purification. MS (ESI, +ve ion) *m/z* 185.1 $(M+1)^+$.

8,8-Difluorooctahydro-1H-pyrido[1,2-a]pyrazine AND 8-fluorooctahydro-1H-pyrido[1,2-a]pyrazine



Step 1: 2-benzyl-8,8-difluorooctahydro-1H-pyrido[1,2-a]pyrazine AND 2-benzyl-8-fluoro-2,3,4,6,7,9a-hexahydro-1H-pyrido[1,2-a]pyrazine AND 2-benzyl-8-fluoro-2,3,4,6,9,9a-hexahydro-1H-pyrido[1,2-a]pyrazine

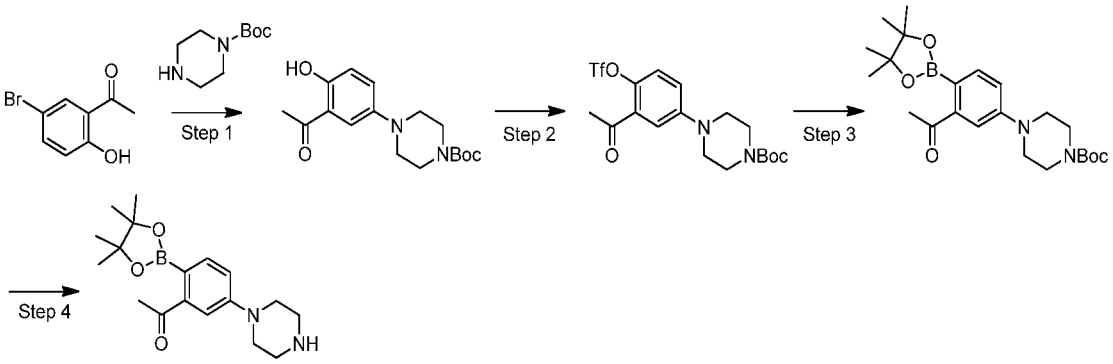
To a stirred solution of 2-benzylhexahydro-1H-pyrido[1,2-a]pyrazin-8(2H)-one (200 mg, 0.819 mmol, AstaTech) in DCM (5.0 mL) cooled in brine-ice bath was added bis(2-methoxyethyl)aminosulfur trifluoride solution (50% in THF,

0.989 mL, 2.456 mmol) dropwise via a syringe. The resulting mixture was stirred for 2 h at -5 °C and 3 h at ambient temperature. The crude mixture was directly loaded onto a silica gel precolumn (25 g) and subjected to flash column chromatography on a 12 g ISCO gold column eluting with 0% to 10 % MeOH/DCM to give 170 mg of a mixture of 2-benzyl-8,8-difluorooctahydro-1H-pyrido[1,2-a]pyrazine, 2-benzyl-8-fluoro-2,3,4,6,7,9a-hexahydro-1H-pyrido[1,2-a]pyrazine, and 2-benzyl-8-fluoro-2,3,4,6,9,9a-hexahydro-1H-pyrido[1,2-a]pyrazine. The mixture was directly used in the next step. MS (ESI, +ve ion) *m/z* 267.2 and 247.2 $(M+1)^+$.

Step 2: 8,8-difluorooctahydro-1H-pyrido[1,2-a]pyrazine AND 8-fluorooctahydro-1H-pyrido[1,2-a]pyrazine

A mixture of 2-benzyl-8,8-difluorooctahydro-1H-pyrido[1,2-a]pyrazine, 2-benzyl-8-fluoro-2,3,4,6,7,9a-hexahydro-1H-pyrido[1,2-a]pyrazine and 2-benzyl-8-fluoro-2,3,4,6,9,9a-hexahydro-1H-pyrido[1,2-a]pyrazine (250 mg, 0.939 mmol) and palladium (5 wt% dry basis on activated carbon, wet, degussa type, spatula tip) in EtOH (25 mL) and concentrated hydrochloric acid (5 mL) was hydrogenated with hydrogen gas at 40-45 psi for a period of 22 h. The reaction was quenched with water (5 mL) and the mixture was filtered through a layer of celite covered with sand. The filtrate was concentrated in vacuo to give 8,8-difluorooctahydro-1H-pyrido[1,2-a]pyrazine AND 8-fluorooctahydro-1H-pyrido[1,2-a]pyrazine as a colorless film which was used without further purification. MS (ESI, +ve ion) *m/z* 177.2 and 159.2 $(M+1)^+$.

1-(5-(Piperazin-1-yl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone



Step 1: tert-butyl 4-(3-acetyl-4-hydroxyphenyl)piperazine-1-carboxylate

To a stirred ice-cooled mixture of 5'-bromo-2'-hydroxyacetophenone (2.000 g, 9.30 mmol, Oakwood), 1-boc-piperazine (2.77 g, 14.88 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.426 g, 0.465 mmol), and 2-(dicyclohexylphosphino)-2'-(n,n-dimethylamino)biphenyl (0.183 g, 0.465 mmol) in THF (20 mL) was added dropwise lithium bis(trimethylsilyl)amide (1.0 M in THF, 32.6 mL, 32.6 mmol). The resulting mixture was stirred at ambient temperature for 10 min before it was placed in an oil bath which was at room temperature. The oil bath was then heated to 70 °C and the reaction mixture was stirred at this temperature for 1.5 h. The mixture was cooled in an ice bath before carefully quenched with ice-cold saturated ammonium chloride aqueous solution. The resulting mixture was poured into a mixture of 1 N aqueous HCl and saturated ammonium chloride aqueous solutions and extracted with 10% MeOH/DCM (2 X). The combined organics were washed with saturated ammonium chloride aqueous solution, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was dissolved in DCM and loaded onto silica gel precolumn and subjected to flash column chromatography on a 40 g ISCO gold column eluting with 0% to 4 % MeOH/DCM to give 1.84 g tert-butyl 4-(3-acetyl-4-hydroxyphenyl)piperazine-1-carboxylate that was directly used in the next step. MS (ESI, +ve ion) *m/z* 321.2 $(M+1)^+$.

Step 2: tert-butyl 4-(3-acetyl-4-(trifluoromethylsulfonyloxy)phenyl)piperazine-1-carboxylate

To a stirred solution of impure tert-butyl 4-(3-acetyl-4-hydroxyphenyl)piperazine-1-carboxylate (1.30 g, 4.06 mmol) and triethylamine (2.258 mL, 16.23 mmol) in DCM (15 mL) was added N-phenyl bis-trifluoromethane sulfonimide (2.90 g, 8.12 mmol) in one portion as a solid. The resulting mixture was stirred at ambient temperature for 2.5 d. The crude mixture was directly loaded onto a silica gel precolumn (25 g) and subjected to flash column chromatography on a 40 g ISCO gold column eluting with 10% to 40 % EtOAc/Hexanes to give tert-butyl 4-(3-acetyl-4-(((trifluoromethyl)sulfonyl)oxy)phenyl)piperazine-1-carboxylate (1.4 g, 3.09 mmol, 76% yield). MS (ESI, +ve ion) *m/z* 475.1 $(M+1)^+$.

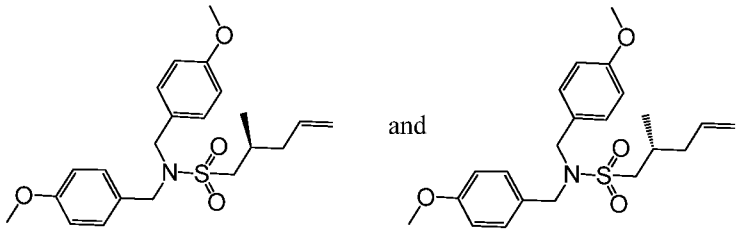
Step 3: tert-butyl 4-(3-acetyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine-1-carboxylate

A 25-mL single-necked round bottom flash previously charged with tert-butyl 4-(3-acetyl-4-(((trifluoromethyl)sulfonyl)oxy)phenyl)piperazine-1-carboxylate (1.17 g, 2.59 mmol), bis(pinacolato)diboron (1.642 g, 6.46 mmol), (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium(II) (0.189 g, 0.259 mmol), and potassium acetate (0.888 g, 9.05 mmol) was subjected to 3 cycles of evacuation and back-filling with nitrogen before 1,4-dioxane (12 mL) was added. The resulting mixture under argon was placed in an oil bath and heated to 50 °C and stirred under argon at this temperature for a period of 20 h. The temperature was lowered to 45 °C and the mixture was stirred overnight at this temperature. The crude reaction mixture was run through a silica gel plug. The filtrate was concentrated in vacuo and the residue was dissolved in DCM and loaded onto silica gel precolumn (25 g) and subjected to flash column chromatography on a 24 g ISCO gold column eluting with 0% to 40% EtOAc/hexanes to give tert-butyl 4-(3-acetyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine-1-carboxylate (380 mg, 0.883 mmol, 34.1% yield) as a solid. MS (ESI, +ve ion) *m/z* 431.3 $(M+1)^+$.

Step 4: 1-(5-(piperazin-1-yl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone

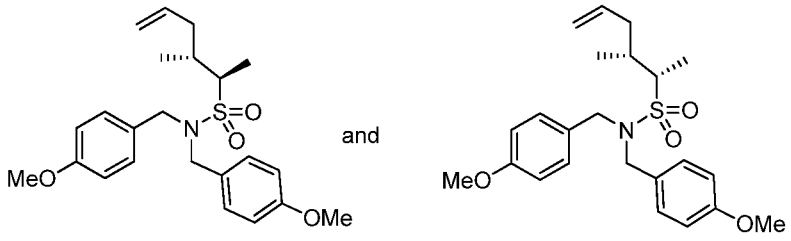
tert-Butyl 4-(3-acetyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine-1-carboxylate in DCM was treated with TFA for the removal the Boc group. 1-(5-(piperazin-1-yl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone was isolated after concentration and used without further purification. MS (ESI, +ve ion) *m/z* 331.2 $(M+1)^+$.

(2S)-N,N-BIS(4-METHOXYBENZYL)-2-METHYLPENT-4-ENE-1-SULFONAMIDE AND (2R)-N,N-BIS(4-METHOXYBENZYL)-2-METHYL-4-PENTENE-1-SULFONAMIDE



The title compound was prepared from Intermediate EE12 and pent-4-en-2-yl 4-methylbenzenesulfonate following a similar procedure described below.

(2R,3R)-N,N-BIS(4-METHOXYBENZYL)-3-METHYLHEX-5-ENE-2-SULFONAMIDE AND (2S,3R)-N,N-BIS(4-METHOXYBENZYL)-3-METHYLHEX-5-ENE-2-SULFONAMIDE

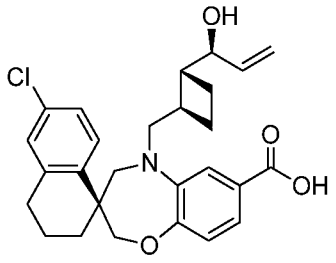


N,N-bis(4-methoxybenzyl)ethanesulfonamide (Intermediate EE13; 1030 mg, 2.95 mmol) was azeotroped in toluene under vacuum for 2 h. Under argon, THF was added and the solution was cooled to -78° C. N-butyllithium solution

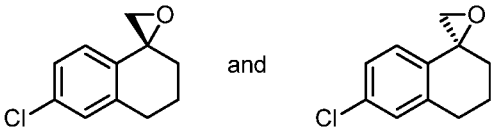
(2.5 M in hexane, 1.533 mL, 3.83 mmol) was then added and the mixture was stirred at -78° C for 60 min. (S)-pent-4-en-2-yl 4-methylbenzenesulfonate (prepared according to the procedure by Sigman, M. S. *et al.*, *J. Am. Chem. Soc.*, **2012**, *134*(28), 11408-11411; 1417 mg, 5.90 mmol) was added as a solution in 3 mL. THF was then added. After 5 min the mixture was allowed to warm to ambient temperature and stirred overnight under argon. The mixture was quenched with satd NH_4Cl and extracted with EtOAc, dried over $MgSO_4$, and concentrated. The crude material was injected into a SiO_2 gel cartridge and purified by chromatography through a 40 g ISCO column, eluting with 5% to 10% to 20% to 40% EtOAc in hexane, to provide a 2.3:1 mixture of the title compounds (420 mg, 1.00 mmol, 34.1% yield).

Intermediate AA11A

(S)-6'-CHLORO-5-(((1R,2R)-2-((S)-1-HYDROXYALLYL)CYCLOBUTYL)METHYL)-3',4,4',5-TETRAHYDRO-2H,2'H-SPIRO[BENZO[B][1,4]OXAZEPINE-3,1'-NAPHTHALENE]-7-CARBOXYLIC ACID

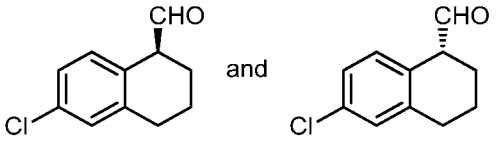


STEP 1: (R)-6-CHLORO-3,4-DIHYDRO-2H-SPIRO[NAPHTHALENE-1,2'-OXIRANE] AND (R)-6-CHLORO-3,4-DIHYDRO-2H-SPIRO[NAPHTHALENE-1,2'-OXIRANE]



A 2L 4-necked-RBF was charged with 6-chloro-3,4-dihydro-1(2H)-naphthalenone (123 g, 681 mmol), trimethylsulfonium iodide (143 g, 701 mmol), and DMSO (1100 mL). KOH (76 g, 1362 mmol) (pellets) was added. The suspension was stirred at ambient temperature for 2 days, after which time crude ^{1}H NMR showed no remaining starting material. The solution was poured into 800 g of crushed ice, rinsed with MTBE (200 mL), and an additional portion of MTBE (700 mL) was added. The resulting mixture was stirred for 5 min and after partition, the bottom aqueous layer was extracted with MTBE twice (500 mL, 300 mL), and combined with the main MTBE extract. The combined organic stream was washed with brine (2X600 mL) and 330 g of Al_2O_3 (neutral) was added. The resulting suspension was stirred for 5 min at 22°C, filtered, and washed with MTBE (400 mL). The filtrate was concentrated to give the product as a red viscous oil (125 g, 94%).

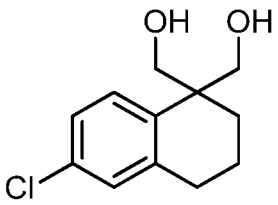
STEP 2: (S)-6-CHLORO-1,2,3,4-TETRAHYDRONAPHTHALENE-1-CARBALDEHYDE AND (R)-6-CHLORO-1,2,3,4-TETRAHYDRONAPHTHALENE-1-CARBALDEHYDE



A 3L 3-necked- RBF was charged with racemic 6-chloro-3,4-dihydro-2H-spiro[naphthalene-1,2'-oxirane] (160 g, 822 mmol) and THF (1760 mL). After the batch was cooled to -8°C with a dry ice/IPA bath, boron trifluoride diethyl etherate (5.07 mL, 41.1 mmol) was added over 3 min. An exotherm raised the batch temp to 10°C instantly. The batch was stirred at -5 to 0°C for 5 min, and LC/MS analysis of a sample (quenched into cold $NaHCO_3$ solution) showed complete conversion. The reaction was quenched by the addition of sat. $NaHCO_3$ (300 mL) at -5°C followed by MTBE (400 mL) and the mixture was transferred to a separatory funnel and rinsed with MTBE (240 mL). After partition, the aqueous layer was discarded along with some white solid (likely boric acid or borax). The

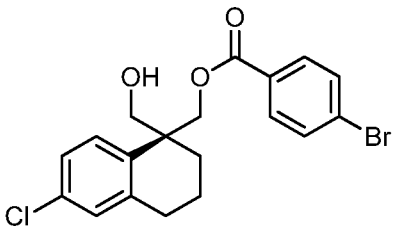
organic layer was washed with brine (350 mL) and concentrated under reduced pressure to give a red oil. The crude material was used directly in Step 4.

STEP 3: (6-CHLORO-1,2,3,4-TETRAHYDRONAPHTHALENE-1,1-DIYL)DIMETHANOL



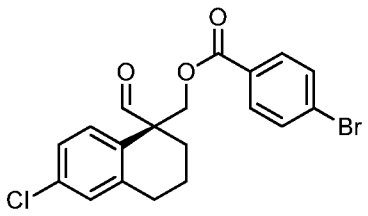
Racemic 6-chloro-1,2,3,4-tetrahydro-1-naphthalenecarbaldehyde was charged onto a 3L 3-necked-RBF and rinsed with diethylene glycol (1000 mL). Formaldehyde (37% solution in H_2O; 652 mL, 8757 mmol) was added and the resulting biphasic emulsion was cooled to 5°C with a dry ice/IPA bath. KOH (45% aqueous solution, 652 mL, 11.9 mol) was added over ~30 min, maintaining the temperature below 20°C. After complete addition, the batch (20°C) was slowly heated to 45°C (Caution: exothermic reaction) and aged for 1 h. HPLC showed complete conversion. Some viscous insoluble tar was formed, which was removed prior to aqueous workup. To the batch was added brine (500 mL) and the mixture was extracted with DCM until the product content in the aqueous phase was less than 5%. The combined DCM extract was concentrated to 750 mL as a red oil, washed with H_2O (500 mL), and the product began to crystallize out. Upon separation, the clear top aqueous layer was discarded and the bottom layer was stirred in ice/ H_2O bath for 30 min, filtered, and washed with DCM (~100 mL) and H_2O (100 mL). The product was dried under dry air/vacuum to give a first crop (113 g, 498 mmol, 57 % yield). The DCM layer from the resulting mother liquor was separated and concentrated to 200-300 g (KF = 0.5%), seeded, and stirred in ice/H_2O bath for 30 min. The product was filtered, washed with DCM (50 mL), and dried in dry air/vacuum to give a second crop (14.3 g, 63.1 mmol, 7 % yield) for a combined total yield of 6-chloro-1,2,3,4-tetrahydronaphthalene-1,1-diyl)dimethanol of 127 g (64%).

STEP 4: (S)-(6-CHLORO-1-(HYDROXYMETHYL)-1,2,3,4-TETRAHYDRONAPHTHALEN-1-YL)METHYL 4-BROMOBENZOATE



To a solution of 2,6-bis((R)-5,5-dibutyl-4-phenyl-4,5-dihydrooxazol-2-yl)pyridine (*R,R*-Kang Catalyst) (1.57 g, 2.64 mmol) in dry DCM (450 mL), copper(II) chloride (0.355 g, 2.64 mmol) was added and the resulting green colored solution was stirred at rt for 1 h. This solution was added via cannula to a solution of (6-chloro-1,2,3,4-tetrahydronaphthalene-1,1-diyl)dimethanol (30 g, 132.73 mmol) in dry DCM (800 mL). The resulting mixture was cooled to -78°C and a light green colored precipitation was observed. A solution of 4-bromobenzoyl chloride (34.77 g, 158.79 mmol) in DCM (500 mL) was then slowly added, followed by the dropwise addition of N-ethyl-N-isopropylpropan-2-amine (20 g, 154 mmol). The resulting reaction mixture was stirred at -78°C for 3 h, then it was quenched with pH 3 phosphate buffer (1 L) and warmed to ambient temperature with vigorous stirring. The mixture was then diluted with DCM (2 L) and the layers were separated. The organic phase was washed with pH 3 buffer (1 L), sat. $NaHCO_3$ (1 L), and brine (2 L) then it was dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by column chromatography over SiO_2 gel (100-200 mesh, 80% DCM in hexane) to afford pure (S)-(6-chloro-1-(hydroxymethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)methyl 4-bromobenzoate (45 g, 84 %; e.r = 91.4:8.6). ChiralCel® OD-H (250 mm x 4.6 mm); Mobile Phase: n-Hexane:IPA: 90:10; Run Time: 20 min; flow rate: 1mL/min; sample preparation: IPA. Retention time (major peak)- 9.32 min; Retention time (minor peak)-11.46 min).

STEP 5: (R)-(6-CHLORO-1-FORMYL-1,2,3,4-TETRAHYDRONAPHTHALEN-1-YL)METHYL 4-BROMOBENZOATE

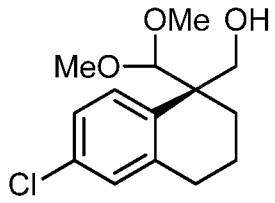


To a stirred solution of (S)-(6-chloro-1-(hydroxymethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)methyl 4-bromobenzoate (100 g, 244.5 mmol) in DCM (2.5 L), Dess-Martin periodinane (121.4 g, 293.3 mmol) was added at 10°C. The cooling bath was removed after addition and the reaction mixture was stirred for 30 min at ambient temperature. H_2O (9 mL) was then added and the resulting biphasic mixture was stirred at ambient temperature for 30 min. The reaction mixture was cooled to 0°C and quenched with 2 L of a 1:1 mixture of 10% $Na_2S_2O_3$/sat. $NaHCO_3$ solution. The reaction mixture was stirred further at ambient temperature for 10 min, then the layers were separated and the aqueous layer was extracted with EtOAc (2 x 1.5 L). The combined organic layer was washed with 1 L of 10% $Na_2S_2O_3$/sat. $NaHCO_3$ solution and 1 L of brine, then it was dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by column chromatography over SiO_2 gel (100-200 mesh, 5% EtOAc/hexane) provided (R)-(6-chloro-1-formyl-1,2,3,4-tetrahydronaphthalen-1-yl)methyl 4-bromobenzoate (80 g, 81%).

The enantiomeric purity of the title compound could be improved by the following procedure: (R)-(6-chloro-1-formyl-1,2,3,4-tetrahydronaphthalen-1-yl)methyl 4-bromobenzoate (190 g) was added in toluene (950 mL) and heated to 50°C to complete dissolution. The homogeneous solution was cooled to ambient temperature and seeded with racemic compound. The solution was cooled to -25°C and aged overnight. The mother liquor was then decanted and concentrated to afford 160 g of enantiomerically enriched (R)-(6-chloro-1-formyl-1,2,3,4-tetrahydronaphthalen-1-yl)methyl 4-bromobenzoate (94% ee as determined by chiral HPLC). Chiral HPLC conditions: Column: ChiralCel® OD-H (250 mm x 4.6 mm); Mobile Phase: n-Hexane:IPA: 90:10. Run Time: 20 min. Flow rate:

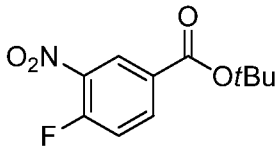
1mL/min. Sample preparation: ethanol. Retention time (major peak): 8.488 min (96.97%); Retention time (minor peak): 9.592 min (3.03%).

STEP 6: (R)-(6-CHLORO-1-(DIMETHOXYMETHYL)-1,2,3,4-TETRAHYDRONAPHTHALEN-1-YL)METHANOL



To a solution of (R)-(6-chloro-1-formyl-1,2,3,4-tetrahydronaphthalen-1-yl)methyl 4-bromobenzoate (75 g, 183.8 mmol) in anhydrous MeOH (1 L), *p*-TsOH (1 g, 9.2 mmol) and trimethyl orthoformate (58.4 mL, 551 mmol) were added and the reaction mixture was refluxed until the starting material was completely consumed (~ 4 h). The reaction mass was concentrated to 50% volume and diluted with THF (1 L) and 1N NaOH (1 L, 1 mol). The resulting reaction mixture was stirred at 40°C overnight and then concentrated under reduced pressure. The residue was diluted with EtOAc (1.5 L). The aqueous layer was separated and extracted with EtOAc (2 x 500 mL) and the combined organic layers were washed with 1N NaOH (1 L) and brine (1 L), dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by column chromatography over 100-200 mesh size SiO_2 gel (10% EtOAc/hexane) to give pure (R)-(6-chloro-1-(dimethoxymethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)methanol as a light brown thick oil (44 g, 89%).

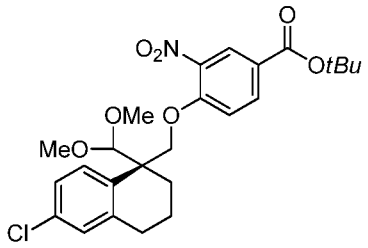
STEP 7: TERT-BUTYL-4-FLUORO-3-NITROBENZOATE



To a solution of 4-fluoro-3-nitrobenzoic acid (100 g, 540.2 mmol) in *t*-butanol (2.5 L), DMAP (13.18 g, 108.04 mmol) and di tert-butyl dicarbonate (248

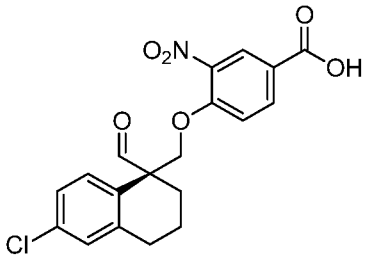
mL, 1080.4 mmol) were added and the reaction mixture was heated at 40°C overnight. Upon completion, the reaction mixture was diluted with H_2O and the aqueous phase was extracted with EtOAc (3 x 1.5 L). The combined organic layer was washed further with H_2O (1x 1L), brine (1x 1L), and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude material thus obtained was purified by column chromatography (100-200 mesh size SiO_2 gel, eluting with a gradient of 100% hexane to 5% EtOAc in hexane) affording pure *tert*-butyl-4-fluoro-3-nitrobenzoate (70 g, 54%) as light yellow solid.

STEP 8: (R)-TERT-BUTYL 4-((6-CHLORO-1-(DIMETHOXYMETHYL)-1,2,3,4-TETRAHYDRONAPHTHALEN-1-YL)METHOXY)-3-NITROBENZOATE



A solution of (R)-(6-chloro-1-(dimethoxymethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)methanol (70 g, 259.2 mmol) in dry THF (3.5 L) was cooled to 0°C and LiHMDS (1 M in THF; 363 mL, 363 mmol) was added dropwise. After 5 min, a solution of tert-butyl 4-fluoro-3-nitrobenzoate (74.9 g, 311 mmol) in THF (500 mL) was added dropwise via dropping funnel and the resulting mixture was warmed to ambient temperature. Upon completion (~1 h), the mixture was cooled to 0°C, quenched with sat. NH_4Cl solution (1 L) and extracted with EtOAc (3 x 1 L). The combined organic layers were washed with NH_4Cl (1 L) and brine (1 L), dried over Na_2SO_4 and concentrated under reduced pressure. The crude material thus obtained was purified by column chromatography using 100-200 mesh size SiO_2 gel (5% EtOAc/hexane) to afford (R)-tert-butyl 4-((6-chloro-1-(dimethoxymethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)methoxy)-3-nitrobenzoate as yellow thick oil (110 g, 87% yield).

STEP 9A: (R)-4-((6-CHLORO-1-FORMYL-1,2,3,4-TETRAHYDRONAPHTHALEN-1-YL)METHOXY)-3-NITROBENZOIC ACID



To a solution of (R)-tert-butyl 4-((6-chloro-1-(dimethoxymethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)methoxy)-3-nitrobenzoate (35 g, 71.25 mmol) in MeCN (1 L), erbium triflate (4.3 g, 7.1 mmol) and H_2O (13 mL) were added. The resulting mixture was heated to 80°C overnight. The solvent was then removed under reduced pressure and the residue was dissolved in Et_2O (1.5 L) and washed with 1N HCl (500 mL) and brine (500 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to afford (R)-4-((6-chloro-1-formyl-1,2,3,4-tetrahydronaphthalen-1-yl)methoxy)-3-nitrobenzoic acid (30 g), which was used without further purification.

Alternatively, (R)-4-((6-chloro-1-formyl-1,2,3,4-tetrahydronaphthalen-1-yl)methoxy)-3-nitrobenzoic acid may be prepared from (6-chloro-1,2,3,4-tetrahydronaphthalene-1,1-diyl)dimethanol (Step 4) as follows:

A 250 mL 3-necked-RBF was charged with copper (II) chloride (0.095 g, 0.02 eq), 2,6-bis((R)-5,5-dibutyl-4-phenyl-4,5-dihydrooxazol-2-yl)pyridine (0.42 g, 0.02 eq) and THF (28.5 g, 4V). After inertion with N_2, the batch was stirred at 20°C for 0.5 h. To the homogenous green solution was added (6-chloro-1,2,3,4-tetrahydronaphthalene-1,1-diyl)dimethanol (8.0 g, 1.00 eq) followed by THF (14.2 g, 2V) and 4-methylmorpholine (3.75 g, 1.05 eq). The reaction mixture was cooled to -20°C, and a solution of 1-napthoyl chloride (7.06 g, 1.05 eq) in THF (21.3 g, 3 V) was added to the batch over 0.5 h maintaining the temperature below -15°C. After aging at -20°C for 20 h, an aliquot of the reaction slurry was sampled and assayed by HPLC. The slurry was directly filtered through a glass-

fritted funnel while maintaining the temperature at -20°C. The filter cake was washed with two portions of cold (<-10°C) THF (2 x 14.2 g, 2V) rinsed through the reaction vessel. The filter cake (4-methylmorpholine•HCl) was transferred to a labeled container. The mother liquor and washes were concentrated to a minimum volume and distillative solvent swap by charging toluene until the batch volume is 6V and toluene/THF ratio is >98:2 (v/v) as measured by QNMR. To the batch at 20°C was added heptane (11 g, 2V) and the slurry was heated to 85°C (dissolution observed). The solution was cooled to 75°C and charged with seed (0.27 g, 0.02 eq). The slurry was cooled to 20°C over 3 h and aged for >1 h. The batch was filtered through a glass-fritted filter and the cake was washed with toluene/heptane (3:1 v/v) (11 g, 2V) then toluene/heptane (1:1 v/v) (11 g, 2V). The cake was dried under N_2 for 12 h at ambient temperature and the cake was assayed dry by QNMR (<1 wt% toluene and heptane). The product was obtained as an off-white solid (8.75 g, 63% after wt adjustment).

A 60L jacketed reactor vented with a bleach scrubber was charged with (S)-(6-chloro-1-(hydroxymethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)methyl 1-naphthoate (2.693 Kg, 88.6 wt%, 6.3 mol) followed by DCM (17.9 Kg, 5 vol) and EtN*i*Pr_2 (2.84 Kg, 3.5 eq). After N_2 inertion, the batch was agitated and cooled to 0°C. To the alcohol slurry mixture in the reactor was added a solution of freshly prepared sulfur trioxide pyridine (2.10 Kg, 2.5 eq of sulfur trioxide pyridine in 7.43 Kg, 3 vol. DMSO) over 30 min while maintaining the batch temperature below 15°C. After addition, HPLC assay showed >99% conversion. The batch was quenched by the addition of H_2O (14 L, 5 vol) over ~20 min. maintaining the batch temperature below 15°C and then toluene (16.8 L, 6 vol) was added. After partition, the organic layer was treated with H_2O (14 L, 5 vol) and toluene (16.8 L, 6 vol). The top organic layer was washed with 2 N HCl twice (14 L each, 5 vol) and brine (14 L, 5 vol). The organic layer was drained to a clean container, assayed by HPLC and then transferred back to the clean 60L reactor through an inline filter. The batch was concentrated to a minimal volume and solvent switched to MeOH until the batch volume was 28 L (10 vol) and MeOH/toluene

ratio was 3:1 (v/v) as measured by QNMR. The batch was then transferred to a 30L jacketed reactor through an inline filter. After adjustment of the batch temperature to 30°C, the batch was seeded with the aldehyde (51 g, 0.02 eq) as a slurry in MeOH (400 mL). After the slurry was aged for 30 min at 30°C, the batch was solvent switched by distillation with MeOH until the batch volume is 11 L (4 vol) and MeOH/toluene ratio is ≥99:1 (v/v). The batch was then cooled to 5°C and MeOH/H_2O mixture (3.70 Kg MeOH + 1.34 Kg H_2O) was added over 1.5 h to bring the total solvent volume to approximately 5.5 vol and final MeOH/H_2O to 90/10 (v/v). The batch was heated to 65°C over 30 min, and cooled to 20°C over 2 h and aged for ~ 2 h. The batch was filtered through an Aurora® filter fitted with ≤ 25 μm filter cloth. The cake was washed with MeOH/H_2O (10:1) (1x2 vol), then MeOH/H_2O (2:1) (1x2 vol). The cake was dried under N_2 at ambient temperature for ≥ 4 h until dry to give the product as an off-white solid (1.99 Kg, 72% after wt% adjustment).

A 3-necked 250mL RBF was charged with (R)-(6-chloro-1-formyl-1,2,3,4-tetrahydronaphthalen-1-yl)methyl 1-naphthoate (10 g, 94.4 wt%, 95.3% LCAP, >99% ee), methanol (100 mL), trimethyl orthoformate (7 mL), and TsOH · H_2O (0.24 g). The RBF was inerted with N_2, and agitation was initiated. The batch was heated to 60 °C and aged for 2 h. HPLC assay showed ≥98% conversion.

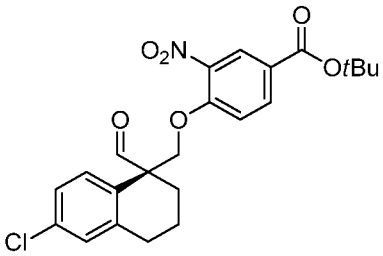
The batch was concentrated under vacuum (~150-190 torr, external temp ~40°C) to minimal volume using a rotoevaporator. The batch was turned over to THF by charging THF three times (50 mL each time) and distilling under vacuum (~165 torr, external temp ~40°C). After each of the first two THF charges, the batch was concentrated down to a minimal volume, and after the last THF charge and distillation QNMR analysis of a sample showed the target ratio of >20/1 THF/MeOH (v/v). LiOH·H_2O (10.46 g, 10 eq) and H_2O (50 mL) were charged to the 3-necked 250mL RBF. The reaction mixture was heated to 65°C and aged for 18 h. HPLC assay showed >99% conversion. The batch was cooled to 20°C and transferred to a 500-mL separatory funnel. MTBE (106 mL) was charged to the separatory funnel and the funnel was shaken well. After settling for 5 min, the

bottom aqueous layer was drained. The top organic layer was washed with 20% K_2CO_3 twice (32 mL and 11 mL). The batch was transferred to a 250mL RBF. Assay by HPLC showed <2% naphthanoic acid by-product. The batch was concentrated to a minimal volume at reduced pressure on the rotoevaporator (300 mbar, external temp ~40°C). The batch was turned over to THF using a rotoevaporator (~250 mbar, external temp ~40°C) by adding and distilling THF (~50 mL, ~50 mL). After each THF charge, the batch was distilled down to a minimal volume. THF (50 mL) was charged to the 250mL RBF. KF of a sample showed 0% H_2O (≤0.1% acceptable). The batch was polish filtered (60mL medium-frit funnel) into a clean and dry 250 mL 3-necked-RBF using THF (50 mL) for rinsing and volume adjusting. To the batch was added 4-fluoro-3-nitrobenzoic acid (4.61 g, 1.0 eq), the mixture was cooled to -20°C, and 20% potassium tert-butoxide THF solution (40 mL) was added over 1.5 h, maintaining the batch temperature at – 20 ± 10°C (exothermic). After complete addition, the batch was aged at -20°C and an aliquot assayed by HPLC after 1.5 h showed 98% conversion. To the batch in the flask was added sat. NH_4Cl solution (10 mL), maintaining the temperature at -20 ± 10°C, followed by addition of H_2O (20 mL) and MeTHF (34 mL) at -20 ± 20°C. The mixture was warmed to 20°C and agitated for 13 h. The batch was transferred to a separatory funnel, allowed to settle for ~5 min, and the bottom aqueous layer was removed keeping the rag with the organic stream. The top organic stream was washed with sat. NH_4Cl solution (10 mL) and H_2O (20 mL) at 20°C. After ~5 min of settling, the aqueous layer was separated. To the total crude organic stream (KF=14%) was added MSA (4 mL) in a 250mL 3-necked-RBF. The batch was heated to reflux (65°C) for 25 h and LC assay showed full conversion (≥97%).

The batch was cooled to <20°C and $K_3PO_4 \cdot H_2O$ (4.5 g) and H_2O (7 mL) were added. The batch was transferred to a separatory funnel and the bottom aqueous layer was drained to give the aldehyde product crude solution. The combined organic crude stream was concentrated to minimum volume using a rotary evaporator. To the batch in a 500mL RBF was charged AcOH (~50 mL,

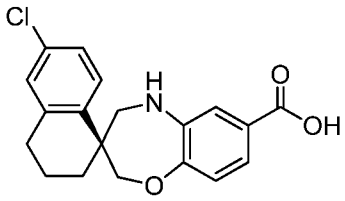
~50 mL) and distilled using a rotary evaporator at reduced pressure (30 mbar, external temp ~40°C). The THF level was measured by QNMR and none was observed. The mixture was transferred to a 250mL 3-necked RBF and AcOH was added to adjust the total volume to ~40 mL, when crystallization occurred. To the batch was added H_2O (12 mL) over ~ 1 h. After aging for >1 h, LC assay of supernatant concentration was 9 mg/mL. If concentration is >10 mg/mL then a small portion of H_2O (0.2 vol) can be added; after checking by LC, repeat if necessary. The batch was filtered, washed with 20% H_2O/AcOH (23 mL) and dried under N_2/vacuum for 3.25 h to give the title compound (8.22 g) as an off-white solid (82% yield corrected for purity).

STEP 9B: (R)-TERT BUTYL 4-((6-CHLORO-1-FORMYL-1,2,3,4-TETRAHYDRONAPHTHALEN-1-YL)METHOXY)-3-NITROBENZOATE



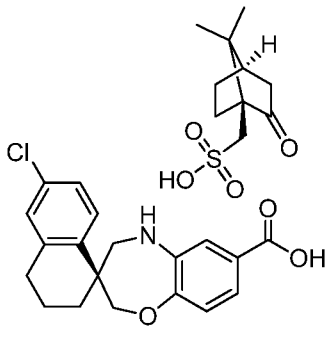
To a solution of (R)-tert-butyl 4-((6-chloro-1-(dimethoxymethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)methoxy)-3-nitrobenzoate (1g, 2.033 mmol) in anhydrous acetone (41 mL) was added amberlyst®-15 (1g, 2.033 mmol; prewashed with 2 x 10 mL dry acetone). The mixture was heated to 50°C for 3.5 h, then filtered and rinsed with DCM. The filtrate was concentrated and dried under high vacuum overnight (it turned a dark red color). LC/MS and NMR analysis suggested ~ 10% of corresponding carboxylic acid was present as well as 0.5 eq mesityl oxide. The mixture was advanced to Step 11 without further purification.

STEP 10: (S)-6'-CHLORO-3',4,4',5-TETRAHYDRO-2H,2'H-SPIRO[BENZO[B][1,4]OXAZEPINE-3,1'-NAPHTHALENE]-7-CARBOXYLIC ACID



A solution of crude (R)-4-((6-chloro-1-formyl-1,2,3,4-tetrahydronaphthalen-1-yl)methoxy)-3-nitrobenzoic acid (30 g, 77.10 mmol) in AcOH (1 L) was heated to 70°C and iron powder (28 g, 500 mmol) was added. The resulting mixture was heated for ~4 h at 70°C. AcOH was then removed under reduced pressure and the residue was dissolved in DCE (1 L). Sodium triacetoxy borohydride (46.5 g, 740 mmol) was added portion-wise and the reaction mixture was stirred at ambient temperature for 1 h. The reaction was then quenched with H_2O followed by 10% aqueous citric acid (500 mL). The aqueous phase was extracted with DCM (2 x 1 L) and the combined organic layer was washed with brine (500 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography using 100-200 mesh size SiO_2 gel (40% EtOAc/hexane) to afford pure (S)-6'-chloro-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylic acid as white solid (24 g, 99% after two steps).

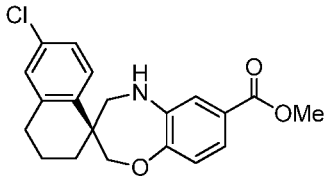
Alternatively, (S)-6'-chloro-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylic acid with ((1S,4R)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonic acid (1:1) may be prepared as follows:



A pressure reactor was charged with (R)-4-((6-chloro-1-formyl-1,2,3,4-tetrahydronaphthalen-1-yl)methoxy)-3-nitrobenzoic acid (20 g, 94 wt%), 5%Pt/S/C wet (2.2 g), THF (400 mL) and titanium isopropoxide (0.5 mL). The reactor was sealed, purged with inert gas (3 cycles, at least once with stirring), and then purged with H_2 (1 cycle). The reactor was pressurized with H_2 to 70 psig, stirring (950 rpm) was initiated, and the temperature was increased to 90 °C maintaining the H_2 pressure in the reactor (70 psig at 22-30 °C, 80 psig at 50-60 °C and 90 psig at 88-91 °C). After 16 h, the reactor was cooled to ambient temperature and purged with inert gas (3 cycles). HPLC analysis of the reaction confirmed > 98% conversion.

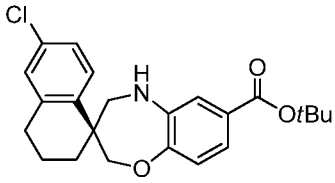
The reaction mixture was filtered through a Celite® pad (2 inch) using additional THF for rinses, and the filtrate was concentrated under reduced pressure at 40 °C. To the residue was added IPA (60 mL) and 2-4% aqueous MeOH (10 mL). The mixture was stirred for 10 min and then it was filtered through a Celite® pad (2 inch). MeOH was evaporated under reduced pressure at 40 °C and to the concentrated IPA solution cooled to ambient temperature was added a solution of +CSA (56.0 g) in IPA (200 mL) dropwise over 2 h. After 10% of the CSA solution has been added, the mixture was seeded with crystals of the title compound (10 - 15 mg) followed by the addition of the remaining CSA solution. After stirring at ambient temperature overnight, the mixture was filtered, and the filter cake was washed with 100 mL of IPA and dried under vacuum/N_2 at ambient temperature. The product is isolated as a white solid:(S)-6'-chloro-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylic acid with ((1S,4R)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonic acid (1:1) (85 - 88% yield, > 99.5% ee).

STEP 11A: (S)- METHYL 6'-CHLORO-3',4,4',5-TETRAHYDRO-2H,2'H-SPIRO[BENZO[B][1,4]OXAZEPINE-3,1'-NAPHTHALENE]-7-CARBOXYLATE



To a solution of (S)-6'-chloro-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylic acid (130 g, 379 mmol) in methanol (6 L) was added amberlyst®-15 (130 g, pre-washed with anhydrous methanol) and heated to reflux for 10 h. Amberlyst® was then removed by filtration and rinsed with methanol (3 x 300 mL). The combined filtrate was concentrated and the residue was purified by column chromatography to give pure (S)- methyl 6'-chloro-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylate as a white solid (105 g, 77%). Chiral HPLC conditions: Column: ChiralCel® OD-H (250 mm x 4.6 mm, 5 □m); Mobile Phase: n-Hexane:EtOH: 95:05. Run Time: 25 min. Flow rate: 1mL/min. Retention time (minor peak): 10.162 min (1.98%); Retention time (major peak): 12.292 min (98.02%).

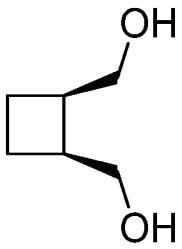
STEP 11B: (S)-TERTBUTYL 6'-CHLORO-3',4,4',5-TETRAHYDRO-2H,2'H-SPIRO[BENZO[B][1,4]OXAZEPINE-3,1'-NAPHTHALENE]-7-CARBOXYLATE



To a solution of (R)-tert-butyl 4-((6-chloro-1-formyl-1,2,3,4-tetrahydronaphthalen-1-yl)methoxy)-3-nitrobenzoate (0.9 g, 2.018 mmol) in AcOH (20.22 mL, 353 mmol) at 70 °C was added iron (0.676 g, 12.11 mmol). The mixture was stirred vigorously for 4 h, then concentrated, and the residue was diluted with 20 mL 1,2-DCE. Sodium triacetoxyhydroborate (1.711 g, 8.07 mmol) was added and the mixture was stirred at ambient temperature for 20 min.

Upon quenching by addition of 20 mL H_2O, a thick slurry was formed. 20 mL 10% citric acid solution was added and the mixture became lighter in color. The layers were separated and the aqueous layer was extracted with 2 x 20 mL DCM. The combined organics were washed with 10 mL 10% citric acid and 10 mL brine, dried over $MgSO_4$, filtered, and concentrated. The residue was deposited on 3 g SiO_2 gel and purified using 5-10% EtOAc in hexane to give (S)-tert-butyl 6'-chloro-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylate (557 mg, 1.393 mmol, 69.0 % yield). Further elution with 30% EtOAc in Hex provided (S)-6'-chloro-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylic acid (132 mg, 0.384 mmol, 19.02 % yield).

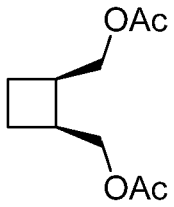
STEP 12: (1R,2S)-1,2-CYCLOBUTANEDIYLDIMETHANOL



To a rapidly stirred solution of LAH (1.0 M solution in THF, 1000 mL, 1000 mmol) at ambient temperature in a 3000 mL 3-necked RBF under a stream of argon, solid (1R,5S)-3-oxabicyclo[3.2.0]heptane-2,4-dione (40 g, 317 mmol) was gradually added over 2 h, maintaining the internal temperature of the reaction mixture below 50°C. The reaction was stirred overnight at ambient temperature under argon. After 16 h, the reaction mixture was cooled by an ice bath to 10°C, and, under a fast stream of argon, a solution of 36 mL H_2O was added drop wise by addition funnel at a rate that maintained the temperature between 12 - 15°C, approximately 1 mL/min, with vigorous stirring (500 rpm). The mixture was then vigorously stirred (500 rpm) in the ice-bath for 1 h, then removed from the bath and stirred to rt for 1 h before cooling again with an ice bath to 5-10°C. To the mixture was added 36 mL of a 15% NaOH aqueous solution over a period of 45

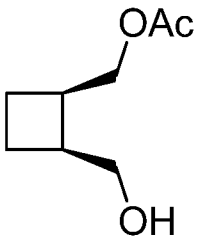
min, maintaining the temperature between 10 - 20°C. To the mixture was added 108 mL H_2O drop wise by addition funnel, maintaining the temperature between 10 - 20°C, over ~1 h. Upon completed addition of the H_2O, the flask was removed from the ice bath, equilibrated to rt and left to stir vigorously under argon overnight. After stirring for 16 h, the mixture was filtered and the filtrate concentrated under reduced pressure to afford a colorless, slightly opaque oil. The oil was taken up in Et_2O and stirred over anhydrous $MgSO_4$ and filtered through a pad of Celite®. The filtrate concentrated under reduced pressure to afford 32.8 g of a colorless oil, which was used in the next step without further purification (89% yield).

STEP 13: *CIS*-CYCLOBUTANE-1,2-DIYLBIS(METHYLENE) DIACETATE



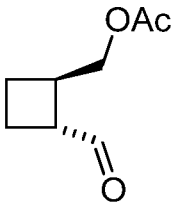
Ac_2O (2.59 mL; 3.0 eq) was added to the *CIS*-1,2-cyclobutanediyldimethanol (1.06 g, 9.15 mmol) and the resulting solution was heated to 50°C. After stirring overnight, the mixture was assayed by GC and showed complete conversion. The mixture was then diluted with 15mL of heptane and concentrated under vacuum to give a clear oil. The oil was dissolved in 15mL heptane and concentrated back down to an oil (azeotropic removal of Ac_2O) to give the title compound as an oil (1.827g, 88% yield, 88.3% purity by QNMR using benzyl benzoate as an internal standard).

STEP 14: ((1R,2S)-2-(HYDROXYMETHYL)CYCLOBUTYL)METHYL ACETATE



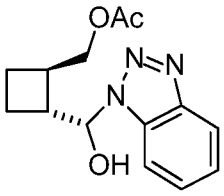
A 12 L 3-neck-RBF equipped with mechanical stirrer was charged with a 1M sodium citrate solution (prepared by mixing sodium citrate tribasic dihydrate; 682 g, 2320 mmol) and H_2O to reach total volume ~2.3 L) and 3.48 L H_2O (~25°C). The mixture was cooled using an ice/H_2O bath to ~20.2°C. pH~8.46 (measured with pH probe). Amano Lipase from *Pseudomonas fluorescens* (41.8 g, 1547 mmol) was then added in one charge (pH ~ 8.12) and the mixture was vigorously stirred at ambient temperature for ~5 min. (1R,2S)-cyclobutane-1,2-diylbis(methylene) diacetate (348 g, 1547 mmol) was added in one charge and the resulting mixture was stirred vigorously at ambient temperature monitoring internal temperature and pH. After stirring the mixture overnight (~20.9°C and pH~5.45) an aliquot was collected, extracted with IPAc, diluted with MeCN and analyzed by GC and the reaction was deemed complete (1.21% SM leftover, 0.17% of enantiomer, 1.8% of diol). Celite® (70 g) added to the reaction mixture and the slurry was filtered through a Celite® pad on a medium porosity glass filter (fast filtration, 15-20 min), rinsing with 2.5 L IPA. The biphasic mixture was transferred into a 12L-extractor and stirred for 1 min. The aqueous layer was separated and extracted with IPAc (1x 4 L), and the combined organic extract was concentrated *in vacuo* obtaining 337.28g (99.6 % *ee*; ~50-60 mol% of residual IPA by ^{1}HNMR; QNMR: 37.63mg + benzyl benzoate (Aldrich catalog#B6630, lot# MKBG9990V, 61.27mg; Result: ~65wt%; corrected yield 89%). The crude product was used as such for the next step.

STEP 15: ((1R,2R)-2-FORMYLCYCLOBUTYL)METHYL ACETATE



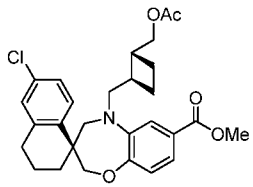
A 2-L Atlas reactor was charged with ((1R,2S)-2-(hydroxymethyl)cyclobutyl)methyl acetate (126.39 g, 79.6 wt% by QNMR; 636 mmol) and 1L of DCM and the jacket temperature was set to 20°C. Iodobenzene diacetate (225 g, 700 mmol) was added as a solid (endothermic addition: the temperature decreased to 15°C). TEMPO (3.97 g, 25.4 mmol) was added as a solid in one portion resulting in a cloudy orange solution, which became clear over the course of 20 min. After stirring at 20°C overnight, an aliquot was collected, diluted with MeOH, and analyzed by GC. An Additional kicker charge of iodobenzene diacetate and TEMPO can be used to push the reaction to completion if necessary. The reaction mixture was then cooled to 1.8°C (internal temperature, ice/dry ice/ H_2O bath) and DIPEA (194 mL, 1113mol) was added drop-wise via addition funnel over 65 min keeping internal temperature <5°C. The cooling bath was removed and the mixture was allowed to warm to ambient temperature with stirring. After 48 h an aliquot was collected, diluted with methanol, and analyzed by GC showing a 12:1 ratio of *trans*: *cis* isomers. The reaction mixture was then cooled to <5°C (ice/ H_2O bath) and H_2O (230 mL) was added over ~10 min (internal temperature reached 14°C). The organic layer was separated, washed with H_2O (125 mL) and 1M aqueous NaH_2PO_4 (90 mL) and concentrated *in vacuo* to afford 273.4 g of ((1R,2R)-2-formylcyclobutyl)methyl acetate (QNMR: 68.85mg + benzyl benzoate (Aldrich catalog# B6630, Lot#MKBG9990V, 72.36mg). The crude product was used as such for next step.

STEP 16: ((1R,2R)-2-((R)-(1H-BENZO[D][1,2,3]TRIAZOL-1-YL)(HYDROXY)METHYL)CYCLOBUTYL)METHYL ACETATE



To a solution of crude ((1R,2R)-2-formylcyclobutyl)methyl acetate (5 g, 10.27 mmol) in 8 mL MTBE was added benzotriazole (1.296 g, 10.00 mmol) as a solid (slightly exothermic). The clear solution became increasingly cloudy and a precipitate formed. The mixture was allowed to equilibrate overnight at ambient temperature then heptane was added (6 mL). After aging for 6 h the mixture was filtered at ambient temperature and washed with 10 mL of 1:1 MTBE/heptane. The white solid was air dried on the frit under vacuum obtaining 2.48 g of ((1R,2R)-2-((R)-(1H-benzo[d][1,2,3]triazol-1-yl)(hydroxy)methyl)cyclobutyl)methyl acetate.

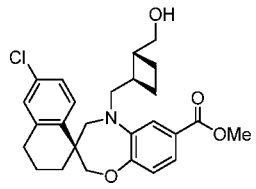
STEP 17: (S)-METHYL 5-(((1S,2R)-2-ACETOXYCYCLOBUTYL)METHYL)-6'-CHLORO-3',4,4',5-TETRAHYDRO-2H,2'H-SPIRO[BENZO[B][1,4]OXAZEPINE-3,1'-NAPHTHALENE]-7-CARBOXYLATE



((1R,2R)-2-Formylcyclobutyl)methyl acetate (from Step 16; 4.36 g, 27.9 mmol) was added to a solution of (S)-methyl 6'-chloro-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylate (5.0 g, 13.97 mmol) (Step 12) in DCM (78 mL) and AcOH (38.8 mL). The solution was stirred at ambient temperature for 10 min, then cooled to 0°C, and sodium cyanoborohydride (1.463 mL, 27.9 mmol) was added slowly over 1 h. The mixture was stirred at 0°C for 10 min, then poured slowly into cold NaOH solution, and extracted with EtOAc (120mL). The organic phase was washed with

brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was loaded to a 220 g ISCO gold column and eluted with 0 % to 10 % EtOAc/hexane to provide the title compound 6.0 g of the title compound as a white solid. m/z (ESI +ve ion) 498.1 $(M+H)^+$.

STEP 18A: (S)-METHYL 6'-CHLORO-5-(((1R,2R)-2-(HYDROXYMETHYL)CYCLOBUTYL)METHYL)-3',4,4',5-TETRAHYDRO-2H,2'H-SPIRO[BENZO[B][1,4]OXAZEPINE-3,1'-NAPHTHALENE]-7-CARBOXYLATE



KOH (0.278 mL, 10.14 mmol) was added to a solution of (S)-methyl 5-(((1R,2S)-2-(acetoxymethyl)cyclobutyl)methyl)-6'-chloro-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylate (from Step 18; 1.530 g, 3.07 mmol) in MeOH (99 mL). The mixture was stirred at ambient temperature for 4 h, then neutralized with 1N HCl to pH = 7, and concentrated under reduced pressure. The aqueous residue was extracted with EtOAc (400 mL) and the organic extract was washed with brine, dried over anhydrous Na_2SO_4, and filtered through a short plug of SiO_2 gel to afford the title compound as a white solid. (1.354 g was obtained. m/z (ESI, +ve ion) 456.2 $(M+H)^+$)

Alternatively, (S)-methyl 6'-chloro-5-(((1R,2R)-2-(hydroxymethyl)cyclobutyl)methyl)-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylate may be prepared as follows:

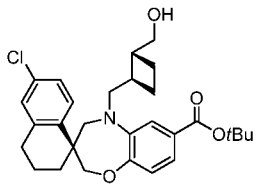
To a slurry of (S)-6'-chloro-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylic acid with ((1S,4R)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonic acid (1:1) (Step 11) (32.22 g, 52.5 mmol) and ((1R,2R)-2-((R)-(1H-benzo[d][1,2,3]triazol-1-

yl)(hydroxy)methyl)cyclobutyl)methyl acetate (Step 17) (15.89 g, 57.7 mmol) in DCM (226 mL, 7 mL/g) was added sodium triacetoxylborohydride (13.90 g, 65.6 mmol) in 4 portions over 30 min. Additional ((1R,2R)-2-((R)-(1H-benzo[d][1,2,3]triazol-1-yl)(hydroxy)methyl)cyclobutyl)methyl acetate (2.89 g, 10.50 mmol) and sodium triacetoxyborohydride (2.78 g, 13.12 mmol) were added to drive the reaction to completion (determined by HPLC assay). 80 mL of H_2O was then added and the resulting mixture was agitated for 5 min. The layers were separated, the organic phase was washed with 60 mL H_2O and 20 mL of brine, and then concentrated to an oil under reduced pressure. The residue was dissolved in 50 mL of MeOH and 40mL of 5N NaOH were then added at ambient temperature (exothermic). Upon reaction completion (determined by HPLC assay), the reaction mixture was partitioned between 133 mL of MTBE and 35mL of 1.5 M citric acid. The organic phase was transferred to a RBF and the solvent was exchanged to MeCN via atmospheric distillation. This solution was seeded at 62°C (a slurry developed), was allowed to reach ambient temperature, and then aged overnight. The slurry was filtered at 20.5°C through a coarse frit glass sinter funnel and the filter cake was washed using 60 mL of MeCN, then dried in a vacuum oven at 40°C to constant weight. Final mass: 21.87g (96.4 w t% by HPLC).

A 100 mL 3-necked-RBF was charged with (S)-6'-chloro-5-(((1R,2R)-2-(hydroxymethyl)cyclobutyl)methyl)-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylic acid (4.53 g, 1.0 eq), MeOH (45 mL, 10 vol), and then a prepared solution of $SOCl_2$ (11.28 mL, 1.0M in MeCN, 1.1 eq). Under an atmosphere of N_2, the batch was heated to 55°C and stirred for 18 h (or until > 99% conversion as determined by HPLC). The reaction mixture was then allowed to cool to 20°C over 2 h. To the resulting white slurry was added Hunig's base (3.94 mL, 2.2 eq) and after aging for 0.5 h, H_2O (9.0 mL, 2 V) was added as antisolvent over 1 h. The white slurry was aged for >2 h and the batch was filtered through a glass-fritted filter and the cake was washed with MeOH/H_2O (5:1 v/v) (9.0 mL, 2V) then MeOH/ H_2O (2:1 v/v) (9.0 mL, 2V). The

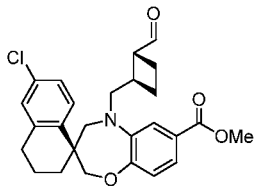
cake was dried under N_2 with vacuum for 12 h at ambient temperature. The product was obtained as a white solid (4.36 g, 92% yield).

STEP 18B: (S)-TERTBUTYL 6'-CHLORO-5-(((1R,2R)-2-(HYDROXYMETHYL)CYCLOBUTYL)METHYL)-3',4,4',5-TETRAHYDRO-2H,2'H-SPIRO[BENZO[B][1,4]OXAZEPINE-3,1'-NAPHTHALENE]-7-CARBOXYLATE



The title compound was synthesized from (S)-tertbutyl 6'-chloro-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylate (Intermediate AA11A) following the procedures described for Intermediate AA11A, Steps 18-19A).

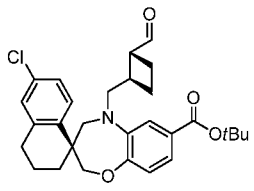
STEP 19A: (S)-METHYL 6'-CHLORO-5-(((1R,2R)-2-FORMYLCYCLOBUTYL)METHYL)-3',4,4',5-TETRAHYDRO-2H,2'H-SPIRO[BENZO[B][1,4]OXAZEPINE-3,1'-NAPHTHALENE]-7-CARBOXYLATE



To a cooled (–70°C) solution of DMSO (7.12 mL, 2.5 eq) and DCM (183 mL, 10 vol) in a 1 L 3-necked- RBF inerted with N_2 was added oxalyl chloride (26.1 mL, 1.0M in DCM, 1.3 eq) at a rate to maintain temperature below –70°C. The batch was aged below –70°C for 30 min and then a prepared solution of (S)-methyl 6'-chloro-5-(((1R,2R)-2-(hydroxymethyl)cyclobutyl)methyl)-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylate

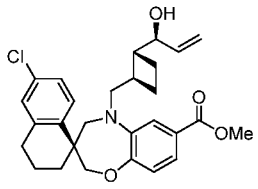
(from Step 19A; 18.3 g, 1.0 eq) in DCM (183 mL, 10 vol) was added at a rate to maintain reaction temperature <–70°C. The batch was aged for 1.5 h and then Et_3N (22.4 mL, 4.0 eq) was added at a rate to maintain batch temperature <–70°C. After aging for 1 h, the batch was allowed to warm to –20°C and H_2O (366 mL, 20 vol) was added. The batch was agitated at 20°C and the phases separated. The organic layer was washed with 2 x 1N HCl (183 mL, 10 vol) and brine (183 mL, 10 vol). The organic layer was polish filtered and concentrated *in vacuo* to afford (S)-methyl 6'-chloro-5-(((1R,2R)-2-formylcyclobutyl)methyl)-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylate (19.91 g, 94% yield corrected for wt%) as a tan foam.

STEP 19B: (S)-TERTBUTYL 6'-CHLORO-5-(((1R,2R)-2-FORMYLCYCLOBUTYL)METHYL)-3',4,4',5-TETRAHYDRO-2H,2'H-SPIRO[BENZO[B][1,4]OXAZEPINE-3,1'-NAPHTHALENE]-7-CARBOXYLATE



The title compound was synthesized from (S)-tertbutyl 6'-chloro-5-(((1R,2R)-2-(hydroxymethyl)cyclobutyl)methyl)-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylate (Intermediate AA 11A, Step 19B) following the procedure described for Intermediate AA11A, step 20A.

STEP 20: (S)-METHYL 6'-CHLORO-5-(((1R,2R)-2-((S)-1-HYDROXYALLYL)CYCLOBUTYL)METHYL)-3',4,4',5-TETRAHYDRO-2H,2'H-SPIRO[BENZO[B][1,4]OXAZEPINE-3,1'-NAPHTHALENE]-7-CARBOXYLATE



An oven dried 3-necked-RBF equipped with a pressure-equalizing addition funnel, thermocouple, and magnetic stirbar was cooled to ambient temperature under a purge of argon gas. The flask was charged with (1*R*,2*S*)-2-morpholino-1-phenylpropan-1-ol (40.2 g, 182 mmol; prepared according to the literature procedure by Brubaker, J.D.; Myers, A.G. *Org. Lett.* **2007**, *9*, 3523-3525) against a positive pressure of argon. The addition funnel was charged with toluene (450 mL), which was dropped into the reactor. The solution was cooled in an ethyleneglycol-CO_2 bath (~ -12°C) and treated with butyllithium solution (2.5 M in hexane, 72.6 mL, 182 mmol), causing a white solid to precipitate that gradually went into solution as it was stirred over 30 min. Divinylzinc solution (605 mL, 182 mmol; prepared according to Brubaker, J.D.; Myers, A.G. *Org. Lett.* **2007**, *9*, 3523-3525. The concentration of divinylzinc solution was determined by titrating against iodine (Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, 890-891; concentration was generally ~0.25M) was added, and the solution was aged with stirring in the cold bath for 1 h; the internal temperature was -15°C. (*S*)-methyl 6'-chloro-5-(((1*R*,2*R*)-2-formylcyclobutyl)methyl)-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylate (from Step 20A; 48.5 g, 107 mmol) (azeotroped thrice with toluene) was added as a solution in toluene (200 mL, 150 mL + 2 x 25 mL cannula/vial rinse) via cannula, over ~ 20 min. The internal temperature rose to -10°C. The mixture was stirred for 90 min while maintaining the internal reaction temperature below -5°C. The addition funnel was charged with 30% w/w aqueous citric acid (450 mL), then the reaction was quenched by adding the solution to the reaction mixture. The reactor was removed from the bath and permitted to stir at ambient temperature. The solution was transferred to a separatory funnel and the flask was rinsed with toluene and 30% aqueous citric acid (50 mL each). The layers were mixed and then separated. The organic layer was washed with H_2O (250 mL), then brine (250 mL), and

finally dried with $MgSO_4$. The solution was filtered and concentrated to yield a yellow oil, ~90 g after vacuum overnight, 20:1 dr. This was split into 3 batches and purified by column chromatography 10 to 20% EtOAc/ hexane 1.5kg SiO_2, to provide (S)-methyl-6'-chloro-5-(((1*R*,2*R*)-2-((*S*)-1-hydroxyallyl)cyclobutyl)methyl)-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylate (43.3 g, 84%). The aqueous layer and washings were placed in an ice/H_2O bath and basified to pH > 13 by addition of 8N aqueous NaOH. This solution was then extracted with toluene (3 x 250 mL). The combined organic extracts were washed with H_2O (250 mL) and brine (250 mL), then dried with $MgSO_4$. The solution was filtered and concentrated to recover the ligand in >95% yield.

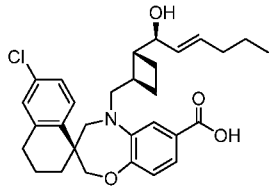
STEP 21: (S)-6'-CHLORO-5-(((1R,2R)-2-((S)-1-HYDROXYALLYL)CYCLOBUTYL)METHYL)-3',4,4',5-TETRAHYDRO-2H,2'H-SPIRO[BENZO[B][1,4]OXAZEPINE-3,1'-NAPHTHALENE]-7-CARBOXYLIC ACID

To a solution of (S)-methyl 6'-chloro-5-(((1R,2R)-2-((S)-1-hydroxyallyl)cyclobutyl)methyl)-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylate (from Step 21; 4.59 g, 9.52 mmol) in a mixture of THF (18 mL), MeOH (6.00 mL) and H_2O (6.00 mL) was added $LiOH{\cdot}H_2O$ (0.799 g, 19.05 mmol) and the reaction was stirred at 50°C for 4 h. The reaction mixture was concentrated to ~ 15 mL, cooled to 0°C and acidified with 2N HCl to pH = 3. The resulting viscous oil was diluted with 20 mL of H_2O and 50 mL of EtOAc and a clear two-layer mixture was obtained. More EtOAc (ca. 200mL) was added and the organic layer was separated, washed with brine, dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was loaded onto a column (220 g), and purified with EtOAc in hexane using the following gradient: 0-2.5 min 0% of EtOAc, 2.5-6 min 0-20% EtOAc, 6-35 min 20-60% EtOAc, 35-40 min 70% EtOAc to give (S)-6'-chloro-5-(((1R,2R)-2-((S)-1-hydroxyallyl)cyclobutyl)methyl)-3',4,4',5-tetrahydro-2H,2'H-

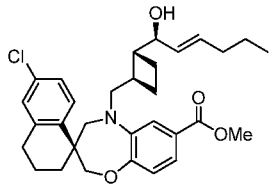
spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylic acid (4.22 g, 9.02 mmol, 95 % yield) as a white solid.

Intermediate AA12A

(S)-6'-CHLORO-5-(((1R,2R)-2-((S,E)-1-HYDROXYHEX-2-EN-1-YL)CYCLOBUTYL)METHYL)-3',4,4',5-TETRAHYDRO-2H,2'H-SPIRO[BENZO[B][1,4]OXAZEPINE-3,1'-NAPHTHALENE]-7-CARBOXYLIC ACID



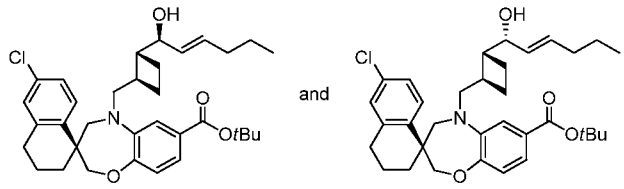
STEP 1A: (S)-METHYL 6'-CHLORO-5-(((1R,2R)-2-((S,E)-1-HYDROXYHEX-2-EN-1-YL)CYCLOBUTYL)METHYL)-3',4,4',5-TETRAHYDRO-2H,2'H-SPIRO[BENZO[B][1,4]OXAZEPINE-3,1'-NAPHTHALENE]-7-CARBOXYLATE



Under argon atmosphere, a dry 3-necked-RBF charged with dry hexane (27 mL) was cooled to 0°C. To this solution was added borane-methyl sulfide complex (3.29 mL, 34.6 mmol) and cyclohexene (7.01 mL, 69.3 mmol) and the mixture was stirred at 0°C for 2 h. To the resulting white suspension was added 1-pentyne (3.41 mL, 34.6 mmol) and the mixture was stirred at ambient temperature for 0.5 h. The mixture was then cooled to -78°C and diethylzinc, 1.0 M solution in hexane (32.3 mL, 32.3 mmol) was added. After addition the mixture was warmed to 0°C, stirred for 3 min then recooled to -78°C. This solution was named solution A. A separate flask was charged with a mixture of

((*S*)-methyl 6'-chloro-5-(((1*R*,2*R*)-2-formylcyclobutyl)methyl)-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylate (Intermediate AA11A, Step 20A, 5.24g, 11.54 mmol) and (2s)-3-exo-(morpholino) isoborneal (0.486 g, 2.032 mmol) in hexane (50.9 mL) and toluene (16.97 mL). The mixture was stirred at ambient temperature until all solid was dissolved, then cooled to 0°C. Under argon atmosphere 54 mL of solution A was added slowly via syringe during 1.6 h. After stirring for 5 min at 0°C, the mixture was quenched with sat. NH_4Cl solution (70 mL), diluted with H_2O (30 mL) and extracted with EtOAc (3 x 270 mL), washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was loaded to a 330 g ISCO gold column and eluted with 0% to 5% EtOAc/hexane, to provide the title compound 3.8 g as a white solid. m/z (ESI, +ve ion) 524.1 $(M+H)^+$.

STEP 1B: (S)-TERTBUTYL 6'-CHLORO-5-(((1R,2R)-2-((S,E)-1-HYDROXYHEX-2-EN-1-YL)CYCLOBUTYL)METHYL)-3',4,4',5-TETRAHYDRO-2H,2'H-SPIRO[BENZO[B][1,4]OXAZEPINE-3,1'-NAPHTHALENE]-7-CARBOXYLATE AND (S)-TERTBUTYL 6'-CHLORO-5-(((1R,2R)-2-((R,E)-1-HYDROXYHEX-2-EN-1-YL)CYCLOBUTYL)METHYL)-3',4,4',5-TETRAHYDRO-2H,2'H-SPIRO[BENZO[B][1,4]OXAZEPINE-3,1'-NAPHTHALENE]-7-CARBOXYLATE



The title compound was synthesized from (S)-tert-butyl 6'-chloro-5-(((1R,2R)-2-formylcyclobutyl)methyl)-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylate (3.19 g, Intermediate AA11A, Step 20B) following the procedure described for Intermediate AA12A, Step 1A. The crude material was absorbed onto a plug of SiO_2 and purified on a 330 g ISCO gold column eluting with 0 to 15 % EtOAc in

heptanes over 45 min to provide (S)-tertbutyl 6'-chloro-5-(((1R,2R)-2-((S,E)-1-hydroxyhex-2-en-1-yl)cyclobutyl)methyl)-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylate (2.36 g). Further elution provided (S)-tert-butyl 6'-chloro-5-(((1R,2R)-2-((R,E)-1-hydroxyhex-2-en-1-yl)cyclobutyl)methyl)-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylate (0.45 g).

STEP 2: (S)-6'-CHLORO-5-(((1R,2R)-2-((S,E)-1-HYDROXYHEX-2-EN-1-YL)CYCLOBUTYL)METHYL)-3',4,4',5-TETRAHYDRO-2H,2'H-SPIRO[BENZO[B][1,4]OXAZEPINE-3,1'-NAPHTHALENE]-7-CARBOXYLIC ACID

A mixture of (S)-methyl 6'-chloro-5-(((1R,2R)-2-((S,E)-1-hydroxyhex-2-en-1-yl)cyclobutyl)methyl)-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylate (from Intermediate AA12A, Step A; 4.6 g, 8.78 mmol) and $LiOH \cdot H_2O$ (3.68 g, 88 mmol) in MeOH (98 mL) and THF (98 mL) (with a few drops of H_2O) was stirred at 50°C overnight. The solvent was removed and the residue was acidified with 1N HCl to pH 2-3. The mixture was extracted with EtOAc (80 mL x 3) and the combined organic layer was washed with brine (10 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give (S)-6'-chloro-5-(((1R,2R)-2-((S,E)-1-hydroxyhex-2-en-1-yl)cyclobutyl)methyl)-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylic acid (4.25 g, 8.34 mmol, 95 % yield).

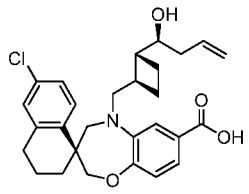
Alternatively, the title compound may be synthesized as follows:

To a solid mixture of (S)-tert-butyl 6'-chloro-5-(((1R,2R)-2-((S,E)-1-hydroxyhex-2-en-1-yl)cyclobutyl)methyl)-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylate (Intermediate AA12A, Step 1B, first eluting isomer, 4.50 g 7.95 mmol) and $LiOH \cdot H_2O$ (1.66 g, 39.7 mmol) was added solvent dioxane/MeOH (1:1) (159 mL). The mixture was heated to 65°C and stirred overnight. The mixture was then diluted with H_2O and

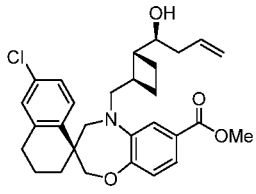
acidified with 1.0 N HCl to pH~4. The organic solvents were evaporated under reduced pressure and to the residue was added H_2O. The aqueous mixture was then extracted with EtOAc three times, and the combined organic extract was concentrated. The residue was purified on a 120 g SiO_2 gel column eluting with a gradient of 0-70% EtOAc in hexane to provide (S)-6'-chloro-5-(((1R,2R)-2-((S,E)-1-hydroxyhex-2-en-1-yl)cyclobutyl)methyl)-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylic acid (3.80 g, 7.45 mmol, 94 % yield).

Intermediate AA13A

(S)-6'-CHLORO-5-(((1R,2R)-2-((S)-1-HYDROXYBUT-3-EN-1-YL)CYCLOBUTYL)METHYL)-3',4,4',5-TETRAHYDRO-2H,2'H-SPIRO[BENZO[B][1,4]OXAZEPINE-3,1'-NAPHTHALENE]-7-CARBOXYLIC ACID



STEP 1A: (S)-METHYL 6'-CHLORO-5-(((1R,2R)-2-((S)-1-HYDROXYBUT-3-EN-1-YL) CYCLOBUTYL)METHYL)-3',4,4',5-TETRAHYDRO-2H,2'H-SPIRO[BENZO[B][1,4] OXAZEPINE-3,1'-NAPHTHALENE]-7-CARBOXYLATE

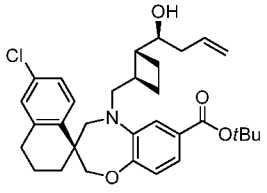


An oven-dried 200-mL flask charged with a suspension of (1R,2R)-N-methyl-1-phenyl-1-(((1S,5S,10R)-10-(trimethylsilyl)-9-borabicyclo[3.3.2]decan-9-yl)oxy)propan-2-amine (5.40 g, 14.54 mmol) in Et_2O (73 mL) under argon was

cooled to -78°C and treated with allylmagnesium bromide (13.22 mL, 13.22 mmol) solution, dropwise. The mixture was allowed to warm to ambient temperature and stirred for 1 h. The solution (~ 0.17 M; solution A) was then recooled to -78°C.

A separate 200 mL flask charged with ((*S*)-methyl 6'-chloro-5-(((1*R*,2*R*)-2-formylcyclobutyl)methyl)-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylate (Intermediate AA11A, Step 20A, 2.0 g, 4.41 mmol) in Et_2O (22.03 mL) under argon was cooled to -78°C. To this solution was added 40 mL of the above-referenced solution A and the resulting mixture was stirred at -78°C for 40 min. 4-methylmorpholine 4-oxide (3.10 g, 26.4 mmol) was then added and the mixture was allowed to warm to ambient temperature for 10 min. Methanol (10 mL) was added and the volatile organics were evaporated under reduced pressure at ambient temperature. Additional methanol (100 mL) was added and after stirring at ambient temperature for 1 h the mixture was concentrated. The residue was diluted with EtOAc (450 mL), washed with 1N HCl (15 mL), Na_2CO_3 solution (10 mL), and brine (6 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was loaded to a 220 g ISCO gold column and eluted with 0% to 5% EtOAc/hexane, to provide 1.88 g of the title compound as a white solid. m/z (ESI, +ve ion) 496.0 $(M+H)^+$.

STEP 1B: (S)-TERTBUTYL 6'-CHLORO-5-(((1R,2R)-2-((S)-1-HYDROXYBUT-3-EN-1-YL) CYCLOBUTYL)METHYL)-3',4,4',5-TETRAHYDRO-2H,2'H-SPIRO[BENZO[B][1,4] OXAZEPINE-3,1'-NAPHTHALENE]-7-CARBOXYLATE



The title compound was synthesized from (S)-tert-butyl 6'-chloro-5-(((1R,2R)-2-formylcyclobutyl)methyl)-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylate (Intermediate AA11A, Step 20B; 3.0 g) following the procedure described for Intermediate AA13A, Step 1A. The crude material was purified on a 220 g SiO_2 gel column eluting with 5% EtOAc in hexane over 60 min to provide (S)-tert-butyl 6'-chloro-5-(((1R,2R)-2-((S)-1-hydroxybut-3-en-1-yl)cyclobutyl)methyl)-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylate (2.19 g).

STEP 2: (S)-6'-CHLORO-5-(((1R,2R)-2-((S)-1-HYDROXYBUT-3-EN-1-YL)CYCLOBUTYL)METHYL)-3',4,4',5-TETRAHYDRO-2H,2'H-SPIRO[BENZO[B][1,4]OXAZEPINE-3,1'-NAPHTHALENE]-7-CARBOXYLIC ACID

A mixture of (S)-methyl 6'-chloro-5-(((1R,2R)-2-((S)-1-hydroxybut-3-en-1-yl)cyclobutyl)methyl)-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylate (from Intermediate AA13A, Step 1A; 1.88 g, 3.79 mmol) and LiOH solution (1M) (34.1 mL, 34.1 mmol) in MeOH (34 mL) and THF (50 mL) was stirred at 65°C for 50 min. After cooling to ambient temperature, the mixture was acidified with 1N HCl to pH 2 to 3, extracted with EtOAc (350 mL), dried over anhydrous Na_2SO_4 and concentrated to provide 1.82 g of the title compound as a white solid. m/z (ESI, +ve ion) 482.0 $(M+H)^+$.

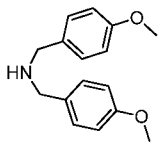
Alternatively, the title compound may be synthesized as follows:

To a solution of (S)-tert-butyl 6'-chloro-5-(((1R,2R)-2-((S)-1-hydroxybut-3-en-1-yl)cyclobutyl)methyl)-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylate (Intermediate AA13A, Step 1B; 250 mg, 0.465 mmol) in DCM (3.717 mL) at ambient temperature, TFA (0.929 mL) was added and the reaction mixture was stirred for 4 h. The crude reaction mixture was then concentrated, the residue was taken up

in EtOAc, washed once with sat. $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated to give a white foam. The crude material was used as such, without further purification.

Intermediate EE11

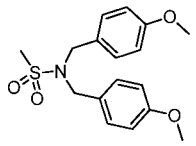
N,N-BIS(4-METHOXYBENZYL)AMINE



A solution of 4-methoxybenzaldehyde (Spectrochem; 100 g, 734.5 mmol) and 4-methoxybenzyl amine (G.L.R.;100 g, 734.5 mmol) in toluene (0.8 L) was refluxed at 130 °C using a Dean-Stark apparatus for 6 h. The reaction was monitored by TLC and upon completion, excess solvent was removed under reduced pressure and the residue was dissolved in methanol (0.8 L). The resulting solution was cooled to 0°C and sodium borohydride (36.12 g, 954.8 mmol) was added in portions. After complete addition, the reaction mixture was stirred for 3 h at ambient temperature. Methanol was removed, and the residue was diluted with H_2O (1.0 L) and EtOAc (2.0 L). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 1.0 L). The combined organic layer was washed with H_2O, brine, and dried over Na_2SO_4. Solvent was removed under reduced pressure and the crude material obtained was purified by column chromatography over SiO_2 gel (100-200 mesh size) eluting with a gradient of 100% hexane to 25% EtOAc in hexane affording the title compound (160 g, 84.6%) as a colorless but opaque liquid.

Intermediate EE12

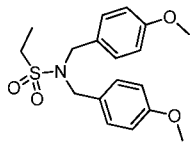
N,N-BIS(4-METHOXYBENZYL)METHANESULFONAMIDE



A mixture of methanesulfonamide (Sigma-Aldrich, 5 g, 52.6 mmol), p-methoxybenzyl chloride (14.98 mL, 110 mmol), K_2CO_3 anhydrous (36.3 g, 263 mmol) and potassium iodide (0.873 g, 5.26 mmol) in anhydrous 2-butanone (175 mL) was refluxed (75°C) overnight. The reaction was monitored by TLC and LC/MS and upon completion, the mixture was cooled to ambient temperature, filtered, washed with Et_2O and concentrated. The crude material (17.54 g, 52.3 mmol, 99 % yield) was used with no further purification. MS (ESI, positive ion) m/z: 358.1 (M+Na).

Intermediate EE13

N,N-BIS(4-METHOXYBENZYL)ETHANESULFONAMIDE

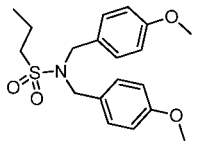


To a solution of N,N-bis(4-methoxybenzyl)amine (Intermediate EE11; 200 g, 775.19 mmol) in DCM (2.5 L) was added Et_3N (336.17 mL, 2325.5 mmol), and the reaction mixture was cooled to 0 °C. Ethanesulfonyl chloride (95 mL, 1007.75 mmol) was added in drop-wise manner followed by DMAP (19.0 g, 155.03 mmol). The resulting reaction mixture was stirred at ambient temperature for 30 min. The reaction was monitored by TLC and upon completion, the mixture was diluted with H_2O and the layers were separated and the aqueous phase was extracted with DCM (3 x 1.5 L). The combined organic layer was washed with H_2O, brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford the crude material which was purified by column chromatography over SiO_2 gel (100-200 mesh), eluting with a gradient of 0-12%

EtOAc in hexane affording the title compound (145 g, 53.4%) as a white fluffy solid.

Intermediate EE14

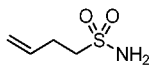
N,N-BIS(4-METHOXYBENZYL)PROPANESULFONAMIDE



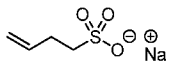
To a solution of N,N-bis(4-methoxybenzyl)amine (Intermediate EE11; 405 g, 1569.7 mmol) in DCM (4.0 L) was added Et_3N (681.0 mL, 4709.3 mmol), and the reaction mixture was cooled to 0 °C. Propanesufonyl chloride (231 mL, 2040.6 mmol) was added in a drop-wise manner followed by DMAP (38.3 g, 313.9 mmol). The resulting mixture was stirred at ambient temperature for 30 min. The reaction was monitored by TLC and upon completion, the mixture was diluted with 2.0 L of H_2O, the layers were separated and the aqueous phase was extracted with DCM (3 x 2.0 L). The combined organic layer was washed with H_2O, brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford the crude material which was purified by column chromatography over SiO_2 gel (100-200 mesh), eluting with a gradient of 0-12% EtOAc in hexane affording the title compound (300 g, 52.44%) as white fluffy solid.

Intermediate EE15

BUT-3-ENE-1-SULFONAMIDE



STEP 1: SODIUM BUT-3-ENE-1-SULFONATE



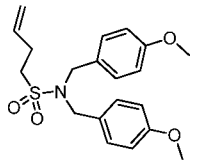
A mixture of 4-bromo-1-butene (LLBChem, 3.01 mL, 29.6 mmol) and sodium sulfite (4.11 g, 32.6 mmol) in H_2O (20 mL) was stirred at 110°C overnight. The reaction was monitored by TLC and upon completion, H_2O was removed under reduced pressure and the residue was triturated with acetone. The solid obtained was filtered to afford the title compound as a white solid (4.53 g) which was used as such in next step.

STEP 2: BUT-3-ENE-1-SULFONAMIDE

A mixture of sodium but-3-ene-1-sulfonate (4.50 g, 28.5 mmol) and phosphorus oxychloride (70 mL) was stirred at 135°C for 7 h. Phosphorus oxychloride was then removed under reduced pressure to obtain a dark residue containing a white solid. This residue was diluted with MeCN (20 mL), and then filtered to remove the precipitate. The filtrate was cooled to 0°C and treated with ammonia solution (30% aqueous) (30 mL) dropwise. After complete addition, the reaction was stirred at 0 °C for 30 min. The mixture was diluted with EtOAc (300 mL), washed with brine, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography over SiO_2 gel (100-200 mesh; eluting with 1:1 EtOAc/hexane), affording the title compound as a white solid (1.55 g, yield: 40%). MS (ESI, positive ion) m/z: 117.1 (M+1).

Intermediate EE16

N,N-BIS(4-METHOXYBENZYL)BUT-3-ENE-1-SULFONAMIDE

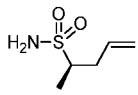


A mixture of but-3-ene-1-sulfonamide (Intermediate EE15; 1.5 g, 11.10 mmol), p-methoxybenzyl chloride (3.76 mL, 27.7 mmol), K_2CO_3 anhydrous (7.67 g, 55.5 mmol) and sodium iodide (0.166 g, 1.110 mmol) in anhydrous 2-butanone (55.5 mL) was refluxed (75°C) overnight. The reaction was monitored by TLC

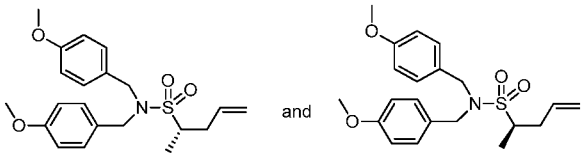
and LC/MS and upon completion, the mixture was cooled to ambient temperature, filtered, and concentrated. The crude material was absorbed onto a plug of SiO_2 gel and purified by chromatography through SiO_2 gel (100-200 mesh), eluting with 0 to 30 % EtOAc in hexane, to provide the title compound (4.10 g, 10.92 mmol, 98 % yield) as a colorless oil. MS (ESI, positive ion) m/z: 376.2 (M+1).

Intermediate EE17

(R)-PENT-4-ENE-2-SULFONAMIDE



STEP 1: (S)-N,N-BIS(4-METHOXYBENZYL)PENT-4-ENE-2-SULFONAMIDE AND (R)-N,N-BIS(4-METHOXYBENZYL)PENT-4-ENE-2-SULFONAMIDE



N,N-bis(4-methoxybenzyl)but-3-ene-1-sulfonamide (Intermediate EE16; 50.0 g, 133.2 mmol) was azeotroped with toluene and dried under vacuum for 1 h. THF (890 mL) was added and the mixture was cooled to -78°C. Butyl lithium (2.5 M in hexane, 63.9 mL, 159.9 mmol) was then added and the reaction mixture was stirred at -78°C for 1h. This anion solution was added slowly to a solution of MeI (16.8 mL, 266.5 mmol) in THF (300 mL) cooled to -78°C. The resulting reaction mixture was stirred for another 15 min at -78°C. On completion of the reaction (monitored by TLC) the mixture was quenched with sat. NH_4Cl solution and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to obtain crude material which was purified by column chromatography over SiO_2 gel eluting with 5-10% EtOAc in hexane to provide the title compound as a racemic mixture (22.0 g) of semisolid nature.

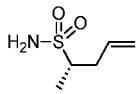
Separation of the enantiomers by SFC (Column: Chiralpak® AD-H, 50 X 250 mm, 5 µm; Mobile Phase A: CO_2; Mobile Phase B: Ethanol; Isocratic: 40% B with CO_2 recycler on; Flow Rate: 200 g/min; Loading: 2.0 mL of sample prepared as above (~100 mg); Detection: UV @ 230 nm; Cycle Time: 5 min; Total Elution Time: 10 min; Instrument: Thar 350 (Lakers)) provided (S)-N,N-bis(4-methoxybenzyl)pent-4-ene-2-sulfonamide as the first eluting isomer (retention time: 2.22 min) and (R)-N,N-bis(4-methoxybenzyl)pent-4-ene-2-sulfonamide as the second eluting isomer (retention time: 2.57 min).

STEP 2: (R)-PENT-4-ENE-2-SULFONAMIDE

To a solution of (R)-N,N-bis(4-methoxybenzyl)pent-4-ene-2-sulfonamide (Intermediate EE17, Step 1, second eluting isomer; 221 mg, 0.567 mmol) in DCM (2.8 mL), was added trifluoroacetic acid (1.7 mL, 22.70 mmol) dropwise (the clear solution very rapidly turned dark). After stirring for 7 h (TLC 30% EtOAc/hexane showed complete loss of starting material) the mixture was diluted with EtOAc, washed with sat. $NaHCO_3$, back extracted with EtOAc, dried over $MgSO_4$, and concentrated. The crude material was purified via chromatography (12 g ISCO gold column; 0-40% EtOAc in hexane) to provide (R)-pent-4-ene-2-sulfonamide (70 mg, 0.469 mmol, 83 % yield)

Intermediate EE172

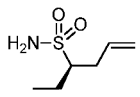
(S)-PENT-4-ENE-2-SULFONAMIDE



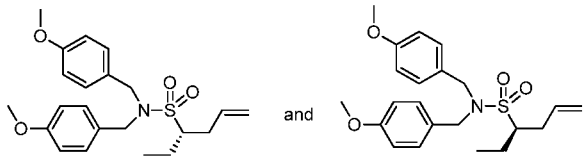
This intermediate was synthesized from (S)-N,N-bis(4-methoxybenzyl)pent-4-ene-2-sulfonamide (Intermediate EE17, Step 1, first eluting isomer) using the procedure described for Intermediate EE17, Step 2.

Intermediate EE18

(R)-HEX-5-ENE-3-SULFONAMIDE



STEP 1: (S)-N,N-BIS(4-METHOXYBENZYL)HEX-5-ENE-3-SULFONAMIDE AND (R)-N,N-BIS(4-METHOXYBENZYL)HEX-5-ENE-3-SULFONAMIDE



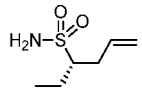
N,N-bis(4-methoxybenzyl)but-3-ene-1-sulfonamide (Intermediate EE16; 40.0 g, 106.6 mmol) was azeotroped in toluene under vacuum for 2 h. THF (700 mL) was added under argon atmosphere and the reaction mixture was cooled to -78°C. Butyl lithium (2.5 M in hexane; 71.6 mL, 127.9 mmol) was added and the reaction mixture was stirred at -78°C for 1h. This anion solution was added slowly to a solution of ethyl iodide (36.44 mL, 340.1 mmol) in THF (40 mL) cooled to -78°C. The resulting reaction mixture was then quenched with sat. NH_4Cl solution, allowed to reach ambient temperature and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to obtain crude material which was purified by column chromatography over SiO_2 gel eluting with 5-10% EtOAc in hexane to provide the title compound as a racemic mixture (24 g) of semisolid nature. MS (ESI, positive ion) m/z; 404.03 (M+1). Separation of the enantiomers by SFC (Sample preparation: 14.4 g/200 mL (72 mg/mL) sample solution in MeOH:DCM (3:1); Column: Chiralpak® AD-H, 30 X 250 mm, 5 µm; Mobile Phase A: CO_2; Mobile Phase B: MeOH (20mM NH_3); Isocratic: 50% B, Flow Rate: 100 mL/min; Outlet Pressure: 100 bar; Loading: 1.0 mL of sample solution prepared as above (72 mg); Detection: UV @ 227 nm; Cycle Time: 8 min; Total Elution Time: 17 min; Instrument: Thar 350 SFC) provided (S)-N,N-bis(4-methoxybenzyl)hex-5-ene-3-sulfonamide as the first eluting isomer and (R)-N,N-bis(4-methoxybenzyl)hex-5-ene-3-sulfonamide as the second eluting isomer.

STEP 2: (R)-HEX-5-ENE-3-SULFONAMIDE

This intermediate was synthesized from (R)-N,N-bis(4-methoxybenzyl)hex-5-ene-3-sulfonamide (Intermediate EE18, Step 1, second eluting isomer) using the procedure described for Intermediate EE17, Step 2.

Intermediate EE182

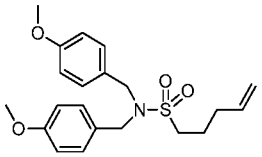
(S)-HEX-5-ENE-3-SULFONAMIDE



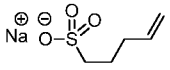
This intermediate was synthesized from (S)-N,N-bis(4-methoxybenzyl)hex-5-ene-3-sulfonamide (Intermediate EE18, Step 1, first eluting isomer) using the procedure described for Intermediate EE17, Step 2.

Intermediate EE19

N,N-BIS(4-METHOXYBENZYL)PENT-4-ENE-1-SULFONAMIDE



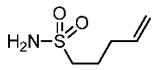
STEP 1: SODIUM PENT-4-ENE-1-SULFONATE



To a 3L 3-necked-RBF equipped with a mechanical stirrer, a N_2 gas inlet, a condenser, and a temperature probe was charged 5-bromo-1-pentene (Sigma Aldrich, 200 g, 1342 mmol), sodium sulfite (Strem Chemicals; 186 g, 1476 mmol), and H_2O (400 mL). The mixture was heated to reflux (set at 100°C and refluxed at 93-94°C) 4 h; aliquot NMR showed >95% conversion. The mixture was concentrated and azeotroped with acetone to remove H_2O. The crude solid

was washed with acetone and filtered to afford sodium pent-4-ene-1-sulfonate (350 g, 2033 mmol).

STEP 2: PENT-4-ENE-1-SULFONAMIDE



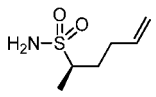
To a 3L 3-necked-RBF equipped with a mechanical stirrer, a N_2 gas inlet, a condenser, and a temperature probe was charged sodium pent-4-ene-1-sulfonate (100 g, 581mmol) (~150 g of crude material from Step 1) and phosphorus oxychloride (Sigma Aldrich; 532 mL, 5808 mmol). The mixture was heated to 90°C for 18 h after which the reaction was filtered and the solid was washed with MeCN. The organic solution was concentrated and azeotroped with MeCN to remove $POCl_3$ to afford 85 g pent-4-ene-1-sulfonyl chloride intermediate. This material (solution in 300 mL MeCN) was charged onto a 1L 3-necked-RBF equipped with a mechanical stirrer, a N_2 gas inlet, a condenser, and a temperature probe. The reaction was cooled to 0-5°C and NH_4OH (Sigma Aldrich; 28 % NH_3; 404 mL, 2904 mmol) was added slowly over 30 min. The reaction was stirred at 0-5°C for 1 h, after which EtOAc (300mL) was added and the mixture was extracted with EtOAc and concentrated to afford pent-4-ene-1-sulfonamide (50 g, 335 mmol, 57.7 % yield) as a brown oil.

STEP 3: N,N-BIS(4-METHOXYBENZYL)PENT-4-ENE-1-SULFONAMIDE

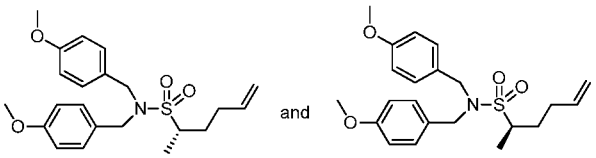
The title compound was synthesized from pent-4-ene-1-sulfonamide (4.5 g, 30.2 mmol) following the procedure described for Intermediate EE16. Purification of the crude material provided N,N-bis(4-methoxybenzyl)pent-4-ene-1-sulfonamide (11.4 g, 29.3 mmol, 97% yield) as a colorless oil.

Intermediate EE20

(R)-HEX-5-ENE-2-SULFONAMIDE



STEP 1: (S)-N,N-BIS(4-METHOXYBENZYL)HEX-5-ENE-2-SULFONAMIDE AND (R)-N,N-BIS(4-METHOXYBENZYL)HEX-5-ENE-2-SULFONAMIDE



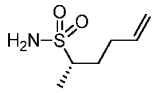
A solution of N,N-bis(4-methoxybenzyl)ethanesulfonamide (Intermediate EE13; 140.0 g, 400.64 mmol) in THF (1.4 L, THF was purged with argon for 15 min before using) was cooled to -78°C and butyl lithium solution (2.6 M in hexane, 200.0 mL, 520.83 mmol) was added drop-wise. The resulting solution was stirred at -78°C for 10 min, and 4-bromo-1-butene (73.2 mL, 721.15 mmol) was added over 2 min. After 5 min, the reaction was allowed to reach ambient temperature and stir for 1 h. The reaction was monitored by TLC and upon completion, the mixture was quenched with sat. NH_4Cl solution (400 mL) and the resulting aqueous layer was extracted with EtOAc (2 x 1.0 L). The combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford the crude material which was purified by column chromatography (SiO_2 gel 100-200 mesh) eluting with a gradient of 0-4% acetone in hexane affording the title compound (racemic mixture, 80.0 g, 49.5%) as a colorless thick oil. MS (ESI, positive ion) m/z: 404.25 (M+1). Separation of the enantiomers by SFC (Sample preparation: 75 g/1.5 L (50 mg/mL) sample solution in MeOH; Column: Chiralpak® IF, 21 X 250 mm, 5 µm; Mobile Phase A: CO_2; Mobile Phase B: MeOH(0.2% DEA); Isocratic: 40% B; Flow Rate: 80 mL/min; Outlet Pressure: 100 bar; Loading: 3.0 mL of sample solution prepared as above (150 mg); Detection: UV at 225 nm; Cycle Time: 3.9 min; Total Elution Time: 6 min; Instrument: Thar 80 SFC) provided (S)-N,N-bis(4-methoxybenzyl)hex-5-ene-2-sulfonamide as the first eluting isomer and (R)-N,N-bis(4-methoxybenzyl)hex-5-ene-2-sulfonamide as the second eluting isomer.

STEP 2: (R)-HEX-5-ENE-2-SULFONAMIDE

The title compound was synthesized from (R)-N,N-bis(4-methoxybenzyl)hex-5-ene-2-sulfonamide (Intermediate EE20, Step 1, second eluting isomer) using the procedure described for Intermediate EE17, Step 2.

Intermediate EE202

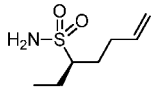
(S)-HEX-5-ENE-2-SULFONAMIDE



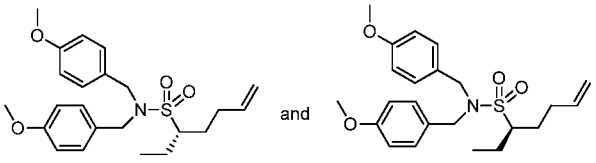
The title compound was synthesized from (S)-N,N-bis(4-methoxybenzyl)hex-5-ene-2-sulfonamide (Intermediate EE20, Step 1, first eluting isomer) using the procedure described for Intermediate EE17, Step 2.

Intermediate EE21

(R)-HEPT-6-ENE-3-SULFONAMIDE



STEP 1: (S)-N,N-BIS(4-METHOXYBENZYL)HEPT-6-ENE-3-SULFONAMIDE AND (R)-N,N-BIS(4-METHOXYBENZYL)HEPT-6-ENE-3-SULFONAMIDE



The title compound was synthesized from N,N-bis(4-methoxybenzyl)propanesulfonamide (Intermediate EE14) using the procedure described for Intermediate AA20, Step 1. Separation of the enantiomers by SFC (Sample preparation: 40.55g/170mL (238.5 mg/mL) sample solution in MeOH;

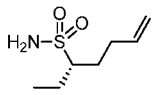
Column: Chiralpak® AD-H, 50 X 150 mm, 5 µm; Mobile Phase A: CO_2; Mobile Phase B: MeOH (20mM NH_3); Isocratic: 50% B; Flow Rate: 190 mL/min; Outlet Pressure: 100 bar; Loading: 1.5 mL of sample solution prepared as above (357.8 mg); Detection: UV at 227 nm; Cycle Time: 17.5 min; Total Elution Time: 21 min; Instrument: Thar 350 SFC) provided (S)-N,N-bis(4-methoxybenzyl)hept-6-ene-3-sulfonamide as the first eluting isomer and (R)-N,N-bis(4-methoxybenzyl)hept-6-ene-3-sulfonamide as the second eluting isomer.

STEP 2: (R)-HEPT-6-ENE-3-SULFONAMIDE

The title compound was synthesized from (R)-N,N-bis(4-methoxybenzyl)hept-6-ene-3-sulfonamide (Intermediate EE21, Step 1, second eluting isomer) using the procedure described for Intermediate EE17, Step 2.

Intermediate EE212

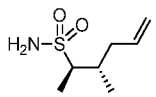
(S)-HEPT-6-ENE-3-SULFONAMIDE



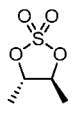
The title compound was synthesized from (S)-N,N-bis(4-methoxybenzyl)hept-6-ene-3-sulfonamide (Intermediate EE21, Step 1, first eluting isomer) using the procedure described for Intermediate EE17, Step 2.

Intermediate EE22

(2R,3S)-3-METHYLHEX-5-ENE-2-SULFONAMIDE

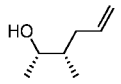


STEP 1: (4S,5S)-4,5-DIMETHYL-1,3,2-DIOXATHIOLANE 2,2-DIOXID



To a 500-mL, 3-necked-RBF (equipped with a H_2O-cooled reflux condenser and an HCl trap) was added (2s,3s)-(+)-2,3-butanediol (Aldrich; 15.00 mL, 166 mmol) and CCl_4 (120 mL). $SOCl_2$, reagentplus (14.57 mL, 200 mmol) was then added drop wise via a syringe over a period of 20 min and the resulting mixture was heated to 98°C for 45 min, then allowed to cool to rt. The reaction mixture was then cooled in an ice/H_2O bath, MeCN (120 mL) and H_2O (150 mL) were added followed by ruthenium(III) chloride (0.035 g, 0.166 mmol). Sodium periodate (53.4 g, 250 mmol) was then added slowly portion wise over 30 min. The resulting biphasic brown mixture was stirred vigorously while allowed to reach rt for a period of 1.5 h (internal temperature never increased above rt). TLC (50% EtOAc in heptanes) showed complete conversion. The crude mixture was then poured into ice H_2O and extracted twice with 300 mL of Et_2O. The combined organic layers were washed once with 200 mL of sat. sodium bicarbonate, washed once with 200 mL of brine, dried over Na_2SO_4, and concentrated by rotary evaporation to give (4S,5S)-4,5-dimethyl-1,3,2-dioxathiolane 2,2-dioxide (21.2 g, 139 mmol) as a red oil.

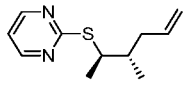
STEP 2: (2S,3S)-3-METHYLHEX-5-EN-2-OL



To a 500 mL flask was added (4S,5S)-4,5-dimethyl-1,3,2-dioxathiolane 2,2-dioxide (from Intermediate EE22, Step 1; 21.2 g, 139 mmol) and THF (220 mL) at which time the solution was cooled to - 78°C and was subjected to 3 cycles of evacuation/back-filling with argon. To the solution was added dilithium tetrachlorocuprate(ii), 0.1M solution in THF (69.7 mL, 6.97 mmol). The resulting mixture was stirred at -78°C for 30 min and then allylmagnesium bromide, 1.0 M solution in Et_2O (397 mL, 397 mmol) was added slowly via cannula over 80 min. The resulting mixture was stirred at 0°C for 4 h. The mixture was quenched with 200 mL H_2O and allowed to reach rt at which time the volatiles were removed by rotary evaporation. To the aqueous residue was then added 50% H_2SO_4 (150 mL), the mixture was stirred for 5 min, Et_2O was then added (400 mL) and the mixture

was stirred vigorously at rt overnight. The layers were separated; the aqueous layer was extracted with 300 mL Et_2O and the combined organic layers were washed with 300 mL of sat. $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated by rotary evaporation to give (2S,3S)-3-methylhex-5-en-2-ol (6.7 g, 58.7 mmol) as a clear oil.

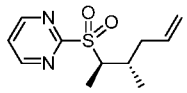
STEP 3: 2-(((2R,3S)-3-METHYLHEX-5-EN-2-YL)THIO)PYRIMIDINE



To a 2000 mL dry RBF containing a stirring solution of tributylphosphine (57.7 mL, 231 mmol) in 1000 mL degassed THF (sparged with argon for 30 min plus 5 cycles of pump/add argon) at 0°C was added diethyl azodicarboxylate (40 wt.% solution in toluene; 103 mL, 262 mmol) drop wise under an atmosphere of argon. A solution of (2S,3S)-3-methylhex-5-en-2-ol (from Intermediate EE22, Step 2; 17.6 g, 154 mmol; dried over Na_2SO_4) was added drop wise as a solution in 50 mL of THF to the solution of phosphine/diethyl azodicarboxylate complex, via syringe-filter (0.45 um). The resulting ROH/diethyl azodicarboxylate/tri-*n*-butylphosphine mixture was aged at zero degrees for 15 min (solution turned light orange), at which time pyrimidine-2-thiol (49.3 g, 439 mmol) was added gradually to the top of the reaction vessel (as a solid) under positive argon pressure. The reaction was stirred at 0°C for 1 h then at rt 15 h (reaction not complete at 12 h by LC/MS). The crude reaction was then filtered to remove excess pyrimidine-2-thiol, diluted with 1000 mL of EtOAc, extracted twice with 500 mL of 1 N K_2CO_3, and once with 500 mL of brine. The aqueous layer was back extracted with 300 mL of EtOAc and the combined organic layers were dried over Na_2SO_4. The organic solution was then filtered, the solvent removed by rotary evaporation and the crude filtered to remove the (E)-diethyl diazene-1,2-dicarboxylategenerated in the reaction. The filtrate (125 g) was passed through a SiO_2 plug (500 g SiO_2, eluting with 2 L of DCM) to give 75 g of crude product after solvent removal. The crude product was

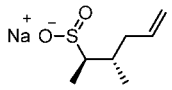
purified again on a Combiflash® (125 g gold SiO_2 column), eluting with 10% EtOAc in heptanes to give 2-(((2R,3S)-3-methylhex-5-en-2-yl)thio)pyrimidine (20.37 g, 98 mmol) as a light yellow oil.

STEP 4: 2-(((2R,3S)-3-METHYLHEX-5-EN-2-YL)SULFONYL)PYRIMIDINE



To a 500 mL 3-necked-RBF with a reflux condenser was added phenylphosphonic acid (3.95 g, 24.96 mmol), sodium tungstate oxide dihydrate (8.23 g, 24.96 mmol), tetrabutylammonium sulfate (50 wt. % solution in H_2O, 28.7 mL, 24.96 mmol), a catalytic amount of hydrogen peroxide (30% in H_2O, 12.75 mL, 125 mmol), toluene (200 mL) and 2-(((2R,3S)-3-methylhex-5-en-2-yl)thio)pyrimidine (from Intermediate EE22, Step 3; 52 g, 250 mmol). The reaction was stirred at 45°C for 5 min at which time hydrogen peroxide 30% in H_2O (58.6 mL, 574 mmol) was added portion wise (10 mL at a time). Five min after the first portion of hydrogen peroxide was added, an exotherm was observed (65°C), the reaction was taken out of oil bath, the addition was stopped and the flask placed in a H_2O bath until temperature stabilizes. The flask was taken out of the H_2O bath and the portion wise addition of hydrogen peroxide was continued at a rate in which the internal temperature stayed between 45°C and 55°C (~ 40 min). An ice bath was utilized if the temperature went above 60°C and an oil bath was used if the temperature fell below 45°C. The reaction was then stirred at 45°C for 1 h. The reaction was diluted with 1400 mL of EtOAc and extracted two times with 500 mL of H_2O and once with 500 mL of brine. The organic layer was dried over Na_2SO_4, filtered, concentrated, and the crude purified on a Combiflash® (330 g gold SiO_2 column per 30 grams of crude), eluting with 0% - 50% EtOAc in heptanes to give 2-(((2R,3S)-3-methylhex-5-en-2-yl)sulfonyl)pyrimidine (55.7 g, 232 mmol) as a light yellow oil.

STEP 5: SODIUM (2R,3S)-3-METHYLHEX-5-ENE-2-SULFINATE



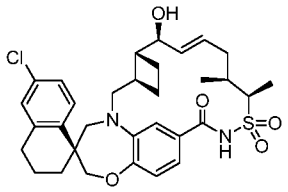
To a solution of 2-(((2R,3S)-3-methylhex-5-en-2-yl)sulfonyl)pyrimidine (from Intermediate EE22, Step 4; 52 g, 216 mmol) in MeOH (400 mL) at rt was added sodium methoxide solution (51.0 mL, 223 mmol) over 70 min. The sodium methoxide was added portion wise, the internal temperature was monitored, and the addition was slowed or the reaction was cooled in a H_2O bath, never letting the internal temperature exceeded 30°C. The mixture was concentrated by rotary evaporation and the waxy solid was triturated with MTBE (add 200 mL MTBE, stir for 1 h using a spatula to break up clumps), filtered (use a stream of N_2 over filter cake), and washed with 100 mL of cold MTBE to obtain sodium (2R,3S)-3-methylhex-5-ene-2-sulfinate (46 g, 250 mmol) as a an off white solid.

STEP 6: (2R,3S)-3-METHYLHEX-5-ENE-2-SULFONAMIDE

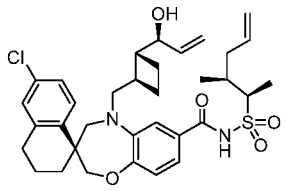
To a 1000 mL 3-necked-RBF was added sodium (2R,3S)-3-methylhex-5-ene-2-sulfinate (from Intermediate EE22, Step 5; 46 g, 225 mmol), 500 mL of H_2O and KOAc (44.1 g, 449 mmol) at rt. The flask was place in a 45°C oil bath and hydroxylamine-O-sulfonic acid (21.09 g, 187 mmol) was added portion wise over 90 min. The internal temperature of the reaction was monitored and the reaction was removed from the oil bath (if needed) to control exotherm (Tmax = 55°C). The reaction was monitored by LC/MS every 10 min and was complete after the addition of 0.83 eq. of hydroxylamine-O-sulfonic acid. The mixture was then cooled to rt and was extracted with 1000 mL of EtOAc. The organic phase was extracted three times with 500 mL of 1 N HCl, two times with 300 mL of sat. sodium bicarbonate, once with 200 mL of brine, dried over Na_2SO_4, filtered, and concentrated by rotary evaporation to provide (2R,3S)-3-methylhex-5-ene-2-sulfonamide (32 g, 181 mmol) as a white solid.

INTERMEDIATE 1

(1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-CHLORO-7'-HYDROXY-11',12'-DIMETHYL-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.$0^{3,6}$.$0^{19,24}$]PENTACOSA[8,16,18,24]TETRAEN]-15'-ONE 13',13'-DIOXIDE



STEP 1: (S)-6'-CHLORO-5-(((1R,2R)-2-((S)-1-HYDROXYALLYL)CYCLOBUTYL)METHYL)-N-(((2R,3S)-3-METHYLHEX-5-EN-2-YL)SULFONYL)-3',4,4',5-TETRAHYDRO-2H,2'H-SPIRO[BENZO[B][1,4]OXAZEPINE-3,1'-NAPHTHALENE]-7-CARBOXAMIDE



DMAP (3.42 g, 28.0 mmol) was added to a solution of (S)-6'-chloro-5-(((1R,2R)-2-((S)-1-hydroxyallyl)cyclobutyl)methyl)-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxylic acid (Intermediate AA11A; 7.7 g, 16.45 mmol) and (2R,3S)-3-methylhex-5-ene-2-sulfonamide (Intermediate EE22; 5.83 g, 32.9 mmol) in DCM (411 mL) cooled to 0°C. EDC hydrochloride (6.31 g, 32.9 mmol) was then added slowly portionwise. The mixture was stirred while allowing to reach ambient temperature overnight. The mixture was washed with 1N HCl and brine and the aqueous layer was back-extracted with EtOAc. The combined organics were dried over $MgSO_4$, filtered and concentrated. The yellow oily residue was loaded onto a 220 ISCO gold column and purified eluting with 0 % to 20 % EtOAc (containing 0.3 % AcOH)/heptanes, to provide (S)-6'-chloro-5-(((1R,2R)-2-((S)-1-

hydroxyallyl)cyclobutyl)methyl)-N-(((2R,3S)-3-methylhex-5-en-2-yl)sulfonyl)-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxamide (7.89 g, 12.58 mmol, 76 % yield).

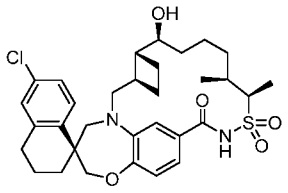
STEP 2: (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-CHLORO-7'-HYDROXY-11',12'-DIMETHYL-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.$0^{3,6}$.$0^{19,24}$]PENTACOSA[8,16,18,24]TETRAEN]-15'-ONE 13',13'-DIOXIDE

To a 20L reactor blanketed in argon was charged 14 L of 1,2-DCE. (S)-6'-chloro-5-(((1R,2R)-2-((S)-1-hydroxyallyl)cyclobutyl)methyl)-N-(((2R,3S)-3-methylhex-5-en-2-yl)sulfonyl)-3',4,4',5-tetrahydro-2H,2'H-spiro[benzo[b][1,4]oxazepine-3,1'-naphthalene]-7-carboxamide (18.75 g, 29.9 mmol) was added as a solution in 400 mL 1,2-DCE followed by a 400 mL rinse. The reactor was sealed and purged with argon. Hoveyda-Grubbs II (1.873 g, 2.99 mmol) was added as a solution in 150 mL of 1,2-DCE followed by a 50 mL rinse. The reactor was heated to 60°C over 1 h with an argon sweep of the headspace and held at temperature for 9 h. The reaction was quenched by the addition of 2-(2-(vinyloxy)ethoxy)ethanol (1.501 g, 11.36 mmol), cooled to ambient temperature, and concentrated to ~ 200 mL volume by rotary evaporation. The reaction was transferred to a 1 L RBF and diluted to 500 mL volume with 1,2-DCE. The reaction was treated with 52 g of Silicycle Si-Thiol (SiliCycle Inc., Quebec City, Quebec CANADA Cat# R51030B) with stirring for 9 h at 40°C, filtered and rinsed with 2 x 65 mL DCM. The solution was passed through a Whatman GF/F filter cup (GE Healthcare Bio-Sciences Pittsburgh, PA, USA) to afford a transparent yellow solution. The reaction was concentrated to afford a crude product mass of 27.4 g. The residue was slurried in 250 mL IPAc and evaporated to dryness three times. The reaction was suspended in 270 mL IPAc, heated to dissolution, allowed to cool to ambient temperature, and stirred for 18. The solids were filtered and washed with 65 mL IPAc. The solid was air-dried for 30 min then placed under high vacuum for 3 h to afford 12.56g of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-

2h,15'h-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.$0^{3,6}$.$0^{19,24}$]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide which is 91.7% by weight. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.06 (s, 1 H), 7.71 (d, *J*=8.56 Hz, 1 H), 7.17 (dd, *J*=8.44, 2.32 Hz, 1 H), 7.09 (d, *J*=2.20 Hz, 1 H), 6.91 (s, 3 H), 5.81 (ddd, *J*=14.92, 7.82, 4.16 Hz, 1 H), 5.71 (dd, *J*=15.41, 8.31 Hz, 1 H), 4.16 - 4.26 (m, 2 H), 3.83 (d, *J*=14.43 Hz, 1 H), 3.69 (d, *J*=14.43 Hz, 1 H), 3.25 (d, *J*=14.43 Hz, 1 H), 3.04 (dd, *J*=15.28, 9.66 Hz, 1 H), 2.68 - 2.84 (m, 2 H), 2.41 (app qd, *J*=9.80, 3.70 Hz, 1 H), 2.25 - 2.34 (m, 1 H), 1.93 - 2.00 (m, 5 H), 1.74 - 2.11 (m, 9 H), 1.62 - 1.73 (m, 1 H), 1.43 (d, *J*=7.09 Hz, 3 H) 1.35 - 1.42 (m, 1 H) 1.03 (d, *J*=6.60 Hz, 3 H). MS (ESI, +ve ion) *m/z* 599.2 $(M+H)^+$.

INTERMEDIATE 2

(1S,3'R,6'R,7'S,11'S,12'R)-6-CHLORO-7'-HYDROXY-11',12'-DIMETHYL-3,4-DIHYDRO-2H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.$0^{3,6}$.$0^{19,24}$]PENTACOSA[16,18,24]TRIEN]-15'-ONE 13',13'-DIOXIDE

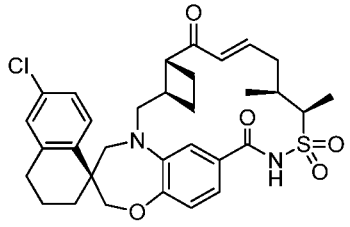


A mixture of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2h,15'h-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.$0^{3,6}$.$0^{19,24}$]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (Intermediate 1, 7.5 mg, 0.013 mmol) and platinum (IV) oxide (2.84 mg, 0.013 mmol) in EtOAc (1.536 mL) was stirred under an atmosphere of H_2 (balloon) at ambient temperature for 45 min. The reaction mixture was then filtered through a syringe filter. The crude material was purified

by chromatography through a Redi-Sep® pre-packed SiO_2 gel column (4 g), eluting with 15 % to 50 % EtOAc (containing 0.3% AcOH)/heptanes, to provide the title product. ^{1}H NMR (400MHz, CD_2Cl_2) δ 8.24 (br. s., 1H), 7.71 (d, J=8.4 Hz, 1H), 7.17 (dd, J=2.3, 8.4 Hz, 1H), 7.09 (d, J=2.2 Hz, 1H), 7.06 (d, J=1.8 Hz, 1H), 6.99 (dd, J=2.0, 8.0 Hz, 1H), 6.93 (d, J=8.2 Hz, 1H), 4.10 (s, 2H), 4.05 (ddd, J=1.2, 7.2, 14.3 Hz, 1H), 3.82 (d, J=15.3 Hz, 1H), 3.74-3.69 (br. S., 1H), 3.68 (d, J=14.3 Hz, 1H), 3.23 (d, J=14.3 Hz, 1H), 3.06 (dd, J=7.3, 15.4 Hz, 1H), 2.84 - 2.68 (m, 2H), 2.38 (d, J=3.5 Hz, 2H), 2.08 - 1.96 (m, 3H), 1.96 - 1.88 (m, 1H), 1.88 - 1.75 (m, 2H), 1.74 - 1.56 (m, 4H), 1.47 (d, J=12.1 Hz, 2H), 1.40 (d, J=7.2 Hz, 3H), 1.32 - 1.26 (m, 2H), 1.23 - 1.15 (m, 2H), 1.00 (d, J=6.8 Hz, 3H). MS (ESI, +ve ion) *m/z* 601.2 $(M+H)^+$.

INTERMEDIATE 3

(1S,3'R,6'R,8'E,12'S)-6-CHLORO-12'-METHYL-3,4-DIHYDRO-2H,7'H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.$0^{3,6}$.$0^{19,24}$]PENTACOSA[8,16,18,24]TETRAENE]-7',15'-DIONE 13',13'-DIOXIDE

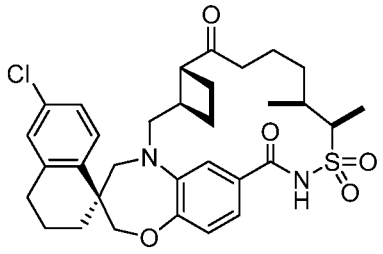


The allyl alcohol (310 mg, 0.520 mmol, Intermediate 1) was dissolved in DCM (6.0 mL) and cooled to 0 °C. Dess-Martin periodinane (270 mg, 0.63 mmol) was then added and the reaction mixture was stirred for 1.5 hours. Another 90 mg of Dess-Martin reagent was added at 0 °C and stirred for an additional 45 minutes. The reaction was quenched with 20 mL of 1M Na_2S2O_3 and allowed to warm to room temperature. The mixture was extracted (3 x 40 mL) with DCM. The combined organic layers were washed with water (1 x 30 mL) and then dried over magnesium sulfate. The crude product was purified by medium pressure

chromatography (silica, 10 to 100% EtOAc (+0.3% HOAc):Hexanes) to give (1S,3'R,6'R,8'E,12'S)-6-chloro-12'-methyl-3,4-dihydro-2H,7'H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.$0^{3,6}$.$0^{19,24}$]pentacosa[8,16,18,24]tetraene]-7',15'-dione 13',13'-dioxide (230 mg, 0.385 mmol, 74.0 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32-9.05 (m, 1H), 7.69-7.90 (m, 1H), 7.35-7.48 (m, 1H), 7.17-7.27 (m, 1H), 7.06-7.16 (m, 1H), 6.81-6.99 (m, 2H), 6.59-6.72 (m, 1H), 5.93 (d, *J*=15.65 Hz, 1H), 4.01-4.24 (m, 3H), 3.74-3.97 (m, 3H), 3.26 (d, *J*=14.48 Hz, 1H), 2.92-3.16 (m, 2H), 2.69-2.89 (m, 2H), 1.70-2.26 (m, 9H), 1.48-1.56 (m, 3H), 1.35-1.46 (m, 1H), 1.29 (t, *J*=7.14 Hz, 1H), 1.07-1.19 (m, 3H). m/z (ESI, +ve ion) 596.7 $(M+H)^+$.

INTERMEDIATE 4

(1S,3'R,6'R,11'S,12'R)-6-CHLORO-11',12'-DIMETHYL-3,4-DIHYDRO-2H,7'H,15'H-SPIRO[NAPHTHALENE-1,22'-[20]OXA[13]THIA[1,14]DIAZATETRACYCLO[14.7.2.$0^{3,6}$.$0^{19,24}$]PENTACOSA[16,18,24]TRIENE]-7',15'-DIONE 13',13'-DIOXIDE



To a solution of (1S,3'R,6'R,7'S,8'E,11'S,12'R)-6-chloro-7'-hydroxy-11',12'-dimethyl-3,4-dihydro-2h,15'h-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.03,6.019,24]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (1.20 g, 2.02 mmol, Intermediate 1) in EtOAc (50 mL) was added platinum (IV) oxide (92 g, 0.40 mmol) and the reaction was fitted with a H_2 balloon and stirred vigorously for 15 h. The reaction mixture was filtered through Celite and concentrated. The concentrate was dissolved in dichloromethane (20 mL) and then Dess-Martin periodinane (0.95 g, 2.2 mmol)

was added in four portions over 5 min at 0 °C. After the reaction was stirred at 0 °C for 15 min, the reaction was quenched with 1N sodium thiosulfate solution at 0 °C (10 mL) and stirred vigorously at rt for 30 min. Then the reaction mixture was extracted (EtOAc). The separated organic layer was washed (brine), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica-gel chromatography (0% to 25% EtOAc/hexane, 0.1% AcOH) to provide (1S,3'R,6'R,11'S,12'R)-6-chloro-11',12'-dimethyl-3,4-dihydro-2H,7'H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo [14.7.2.$0^{3,6}$.$0^{19,24}$]pentacosa[16,18,24]triene]-7',15'-dione 13',13'-dioxide as a solid (0.85 g, 70% yield). MS (ESI, +ve ion) *m/z* 599.2 $(M+H)^+$.

BIOLOGICAL ASSAYS

Cell free Mcl-1:Bim affinity assay (Mcl-1 HTRF)

The inhibition of the Mcl-1/Bim interaction was measured using a time-resolved fluorescence resonance energy transfer (TR-FRET) assay. The recombinant human Mcl-1 (C-terminally 6xHis tagged Mcl-1 containing residues 171-327) was generated at Amgen Inc (Thousand Oaks, CA). A biotinylated peptide derived from human Bim (residues 51-76) was purchased from CPC Scientific (San Jose, CA). The TR-FRET assay was conducted in a 384-well white OptiPlate™ (PerkinElmer, Waltham, MA) in a total volume of 40 µL. The reaction mixture contained 0.1 nM Mcl-1(171-327), 0.05 nM biotin-Bim(51-76), 0.05 nM LANCE® Eu-W1024 Anti-6xHis (PerkinElmer), 0.072 nM Streptavidin-Xlent (Cisbio, Bedford, MA), and serially diluted test compounds in the binding buffer of 20 mM Hepes, pH 7.5, 150 mM NaCl, 0.016 mM Brij®35, and 1 mM dithiothreitol. Test compounds were pre-incubated with Mcl-1(171-327) and biotin-Bim (51-76) for 60 min before addition of the detection mixture (LANCE®Eu-W1024 Anti-6xHis and Streptavidin-Xlent). The reaction plates were further incubated overnight and then were read on an Envision® multimode reader (PerkinElmer). Fluorescence signals were measured at 620 nm (40-nm bandwidth) and 665 nm (7.5-nm bandwidth) with a 60 µs delay after excitation at 320 nm (75-nm bandwidth). The signal ratio at 665/620 nm corresponded to the

Mcl-1/Bim interaction and was used in all data analyses. The IC_{50} values of test compounds were determined from duplicate data by analyzing competition curves using a four-parameter sigmoidal model in GraphPad Prism (GraphPad Software, San Diego, CA) or in Genedata Screener® (Genedata, Basel, Switzerland).

Cell viability assay (OPM-2 10 FBS)

The human multiple myeloma cell line, OPM-2, was cultured in complete growth medium containing RPMI 1640 and 10% fetal bovine serum (FBS). Cells were seeded into 384-well plates at 3000 cells/well density in complete growth medium containing 10% FBS, and incubated for 16 h with serially diluted test compounds in a 37°C incubator with 5% CO_2. Cell viability was tested using CellTiter-Glo® assay (Promega, Madison, WI) according to the manufacturer recommendations. Luminescence was determined using an EnVision® Multilabel plate reader 25 min after the addition of detection reagent. IC_{50} values were then calculated with Xlfit using a logistical 4-parameter fit model in GraphPad Prism (GraphPad Software, San Diego, CA) or in Genedata Screener® (Genedata, Basel, Switzerland).

Results for compounds tested in these biological assays are set forth below in Table 4 and Table 5.

TABLE 4

Example Number	Mcl-1 HTRF IC_{50} (μM)	OPM-2 10% FBS IC_{50} IP (μM)
1	0.000086	0.085
2	0.000109	0.076
3	0.000094	0.060
4	0.000116	0.094
5	0.000098	0.040

6	0.000079	0.076
7	0.000058	0.025
8	0.000053	0.025
9	0.000078	0.050
10	0.000103	0.075
11	0.000098	0.051
12	0.000072	0.022
13	0.000094	0.063
14	0.000080	0.059
15	0.000119	0.071
16	0.000065	0.053
17	0.000073	0.034
18	0.000060	0.022
19	0.000125	0.047
20	0.000082	0.022
21	0.000156	0.047
22	0.000669	2.230
23	0.000071	0.024
24	0.000086	0.035
25	0.000113	0.041
26	0.000079	0.032

27	0.000095	0.029
28	0.000082	0.111
29	0.000249	0.186
30	0.000110	0.166
31	0.000184	0.216
32	0.000128	0.147
33	0.008250	5.570
34	0.000495	0.379
35	0.000218	0.235
36	0.000554	0.518
37	0.000615	0.643
38	0.000342	0.489
39	0.000377	0.389
40	0.000444	0.571
41	0.000642	0.810
42	0.000170	0.149
43	0.001640	0.888
44	0.000288	1.360
45	0.000245	0.891
46	0.000107	0.167
47	0.000131	0.285

48	0.000140	0.407
49	0.000087	0.185
50	0.000736	1.530
51	0.000072	0.099
52	0.000522	0.330
53	0.000336	0.290
54	0.000173	0.129
55	0.000162	0.080
56	0.000083	0.079
57	0.000258	0.090
58	0.000719	0.095
59	0.000116	0.048
60	0.000287	0.129
61	0.000075	0.124
62	0.000115	0.110
63	0.000173	0.582
64	0.000126	0.201
65	0.000451	1.500
66	0.000246	0.318
67	0.000197	0.149
68	0.000397	1.520

69	0.003830	1.480
70	0.001326	3.140
71	0.000371	1.140
72	0.000800	0.185
73	0.000609	0.129
74	0.002290	3.360
75	0.002047	1.610
76	0.003815	0.670
77	0.001217	0.415
78	0.000573	0.175
79	0.001800	0.245
80	0.001550	0.205
81	0.000140	0.112
82	0.000394	0.520
83	0.000223	0.245
84	0.000106	0.061
85	0.000491	0.274
86	0.00390	7.95
87	0.000127	0.141
88	0.000139	0.074
89	0.003750	8.210

90	0.004660	8.980
91	0.000203	0.559
92	0.000143	0.199
93	0.000530	0.924
94	0.000191	0.140
95	0.000189	0.338
96	0.000114	0.111
97	0.000299	0.228
98	0.000373	0.183
99	0.000243	0.310
100	0.000188	1.650
101	0.000196	0.263
102	0.000182	0.416
103	0.000452	0.737
104	0.001119	0.782
105	0.000423	0.655
106	0.000299	0.308
107	0.001138	0.872
108	0.000198	0.116
109	0.001042	0.916
110	0.000505	1.720

111	0.000362	0.301
112	0.000617	0.654
113	0.001190	1.330
114	0.000104	0.068
115	0.001370	0.686
116	0.000244	0.387
117	0.000352	0.358
118	0.000215	0.558
119	0.000465	0.694
120	0.000263	0.304
121	0.000084	0.120
122	0.000087	0.138
123	0.000205	0.228
124	0.000646	0.598
125	0.006100	1.475
126	0.000627	0.900
127	0.000395	6.120
128	0.000256	19.600
129	0.001694	2.630
130	0.000920	1.580
131	0.000249	0.482

132	0.000613	0.263
133	0.000189	0.136
134	0.004640	3.000
135	0.008175	> 33.3
136	0.004700	1.020
137	0.004740	1.150
138	0.026700	> 33.3
139	0.032017	> 33.3
140	0.000098	0.125
141	0.000152	0.367
142	0.000157	0.174
143	0.000432	0.219
144	0.000271	0.163
145	0.000124	0.113
146	0.000337	0.150
147	0.000376	0.157
148	0.001200	1.610
149	0.000128	0.119
150	0.000193	0.245
151	0.000843	0.462
152	0.000092	0.110

153	0.000960	10.800
154	0.000197	0.554
155	0.000228	0.378
156	0.000096	0.062
157	0.000126	0.121
158	0.000092	0.018
159	0.000096	0.079
160	0.000221	0.148
161	0.000094	0.113
162	0.000072	0.055
163	0.000179	0.130
164	0.000047	0.031
165	0.000190	0.182
166	0.000107	0.050
167	0.000086	0.052
168	0.000138	0.052
169	0.000140	0.074
170	0.000131	0.075
171	0.000074	0.122
172	0.000137	0.055
173	0.000173	0.323

174	0.000322	0.639
175	0.000069	0.064
176	0.000118	0.149
177	0.000153	0.615
178	0.000177	0.071
179	0.000072	0.036
180	0.000106	0.081
181	0.000324	0.074
182	0.000171	0.088
184	0.000068	0.017
185	0.000170	1.060
186	0.000255	0.431
187	0.000066	0.043
188	0.000084	0.038
189	0.000084	0.033
190	0.000087	0.053
191	0.000096	0.042
192	0.000078	0.065
193	0.000096	0.023
194	0.000148	0.054
195	0.000214	0.065

196	0.000470	0.304
197	0.000364	0.129
198	0.000181	1.314
199	0.000119	0.208
200	0.000315	0.583
201	0.000119	0.244
202	0.000058	0.142
203	0.000113	0.112
204	0.000230	0.319
205	0.000263	0.437
206	0.000223	6.300
207	0.000137	0.395
208	0.000099	0.368
209	0.000552	0.437
210	0.000138	0.185
211	0.000147	0.156
212	0.000122	0.307
213	0.000239	0.400
214	0.000071	0.084
215	0.000149	0.107
216	0.000490	0.183

217	-	0.192
218	0.000142	0.092
219	0.000073	0.047
220	0.000052	0.042
221	0.000069	0.120
222	0.000080	0.118
223	0.000251	0.258
224	0.000127	0.157
225	0.000087	0.280
226	0.000057	0.049
227	0.000207	0.131
228	0.000200	0.0931
229	0.000619	0.096
230	0.000051	0.070
231	0.000061	0.098
232	0.000141	0.200
233	0.000516	0.202
234	0.000163	0.071
235	0.000180	0.120
236	0.000097	0.087
237	0.000130	0.064

238	0.000176	0.076
239	0.000146	0.148
240	0.000128	0.141
241	0.000150	0.137
242	0.000249	0.791
243	0.000078	0.106
244	0.001654	0.638
245	0.000120	0.058
246	0.000099	0.138
247	0.000129	0.107
248	0.000222	0.518
249	0.000063	0.114
250	0.000071	0.047
251	0.002260	3.870
252	0.001375	1.800
253	0.000804	0.887
254	0.001200	0.544
255	0.001740	1.480
256	0.000433	1.640
257	0.000403	0.981
258	0.000069	0.095

259	0.000230	0.254
260	0.000083	0.103
261	0.000153	0.146
262	0.000093	0.089
263	0.000147	0.124
264	0.000396	0.771
265	0.000423	0.578
266	0.000282	0.723
267	0.000297	0.250
268	0.000065	0.072
269	0.000104	0.086
270	0.000035	4.860
271	0.000031	0.359
272	0.000144	0.137
273	0.000494	0.501
274	0.000285	0.232
275	0.000176	0.082
276	0.000096	0.110
277	0.000058	0.057
278	0.000039	0.574
279	0.000084	0.453

280	0.000052	0.073
281	0.000181	0.152
282	0.000118	0.486
283	0.000354	0.839
284	0.000288	0.230
285	0.000107	0.062
286	0.000155	0.050
287	0.000137	0.050
288	0.000484	0.652
289	0.000214	0.131
290	0.000215	0.149
291	0.000083	0.104
292	0.000356	0.399
293	0.000242	0.207
294	0.000660	0.687
295	0.000321	0.104
296	0.000211	1.310
297	0.000128	0.066
298	0.000279	0.262
299	0.000367	0.456
300	0.000165	0.284

301	0.000196	0.141
302	0.000107	0.084
303	0.000150	0.101
304	0.000226	0.239
305	0.000330	0.327
306	0.000282	0.246
307	0.000087	0.041
308	0.000111	0.070
309	0.000215	0.064
310	0.000117	0.517
311	0.000324	0.362
312	0.000576	0.408
313	0.000225	0.131
314	0.000118	0.126
315	0.000122	0.124
316	0.000166	0.047
317	0.000186	0.088
318	0.000138	0.077
319	0.000081	0.087
320	0.000524	0.302
321	0.000145	0.092

322	0.000145	0.087
323	0.000166	0.169
324	0.000136	0.057
325	0.000180	0.192
326	0.000307	0.488
327	0.000214	0.174
328	0.000087	0.048
329	0.000137	0.243
330	0.000425	0.278
331	0.000184	0.230
332	0.000096	0.089
333	0.000088	0.082
334	0.000186	0.159
335	0.000148	0.133
336	0.000085	0.051
337	0.000090	0.059
338	0.000100	0.057
339	0.000117	0.153
340	0.000128	0.060
341	0.000052	0.042
342	0.000089	0.104

343	0.000093	0.094
344	0.000116	0.057
345	0.000803	1.040
346	0.000062	0.066
347	0.000392	0.871
348	0.002625	5.360
349	0.001610	7.790
350	0.012333	> 33.3
351	0.000121	0.196
352	0.000111	0.162
353	0.000135	0.186
354	0.000214	0.450
355	0.000172	0.272
356	0.000110	0.367
357	0.000067	0.118
358	0.000066	0.144
359	0.002080	> 33.3
360	0.001067	2.410
361	0.000101	0.028
362	0.000061	0.058
363	0.000080	0.101

364	0.192500	> 33.3
365	0.000104	0.032
366	0.000248	0.133
367	0.000201	0.273
368	0.000069	0.068
369	-	0.071
370	-	0.369
371	0.000101	0.043
372	0.000175	0.085
373	0.000069	0.060
374	0.000095	0.041
375	0.000102	0.042
376	0.000152	0.064
377	0.000130	0.055
378	0.001187	1.415
379	0.000220	0.235
380	0.000712	0.338
381	0.000157	0.262
382	0.000130	0.106
383	0.000194	0.182
384	0.000324	0.266

385	0.000762	0.717
386	0.000273	0.211
387	0.000291	0.272
388	0.000069	0.194
389	0.000218	0.278
390	0.000095	0.068
391	0.001120	1.710
392	0.000443	4.610
393	0.000079	1.590
394	0.000533	0.461
395	0.000302	1.960
396	0.000084	1.020
397	0.000532	1.820
398	0.001007	5.585
399	0.000401	2.100
400	0.001100	2.872
401	0.002380	2.170
402	0.001399	0.745
403	0.000472	0.215
404	0.000565	0.319
405	0.000057	0.018

406	0.000304	0.329
407	0.000751	0.567
408	0.000225	4.610
409	0.000214	0.140
410	0.000327	0.247
411	0.000930	0.796
412	0.001410	0.749
413	0.000257	0.145
414	0.000154	1.840
415	0.000294	4.020
416	0.000423	6.910
417	0.001750	6.320
418	0.000662	0.515
419	0.003310	2.140
420	0.000176	0.080
421	0.001175	0.596
422	0.000289	0.405
423	0.000269	0.626
424	-	2.240
425	0.000281	0.086
426	0.001315	2.170

427	0.000208	0.141
428	0.000154	0.316
429	0.000214	0.174
430	0.002475	1.310
431	0.000555	0.206
432	0.000229	0.302
433	0.001186	1.670
434	0.000585	0.913
435	0.000380	0.152
436	0.000156	3.200
437	0.000201	0.080
438	0.000308	0.230
439	0.000427	0.505
440	0.000140	0.038
441	0.000459	0.443
442	0.000221	0.286
443	0.001255	0.555
444	0.000128	0.251
445	0.000282	0.161
446	0.000776	0.446
447	0.000119	0.069

448	0.000315	0.581
449	0.000449	0.290
450	0.000112	0.791
451	0.001006	1.810
452	0.003375	17.200
453	0.000451	0.611
454	0.000174	0.213
455	0.000104	0.110
456	0.001045	0.908
457	0.001468	2.610
458	0.000848	0.439
459	0.000225	0.267
460	0.000147	0.161
461	0.000111	0.218
462	0.000261	0.198
463	0.000439	0.322
464	0.000387	0.426
465	0.000581	0.536
466	0.000900	0.446
467	0.000223	0.173
468	0.001075	1.210

469	0.000075	0.295
470	0.000156	0.122
471	0.000321	0.943
472	0.000167	0.068
473	0.000112	0.025
474	0.000088	0.042
475	0.000411	0.350
476	0.000223	0.173
477	0.000240	0.403
478	0.000423	0.197
479	0.000315	4.980
480	0.000067	0.113
481	0.000212	1.110
482	0.000180	0.590
483	0.000244	0.260
484	0.000075	0.162
485	0.000292	1.210
486	0.000081	0.269
487	0.000221	1.500
488	0.000076	0.183
489	0.000035	0.046

490	0.000288	1.860
491	0.000096	0.453
492	0.000295	0.516
493	0.000109	0.170
494	0.000276	1.480
495	0.000075	0.082
496	0.000105	0.207
497	0.000469	1.210
498	0.000120	0.143
499	0.000355	0.110
500	0.000147	0.078
501	0.000672	5.030
502	0.000069	0.191
503	0.000331	0.200
504	0.000159	0.087
506	0.003800	7.430
507	0.013700	> 33.3
508	0.000248	1.130
509	0.000155	0.744
510	0.000258	1.520
511	0.000493	1.380

512	0.000170	0.363
513	0.000235	0.383
514	0.000279	0.567
515	0.000113	0.120
516	0.000254	0.209
517	0.000259	0.252
518	0.000164	0.224
519	0.000157	0.116
520	0.000128	0.095
521	0.000133	0.174
522	0.000142	0.110
523	0.000158	0.260
524	-	0.135
525	0.000142	0.087
526	0.000144	0.289
527	0.000804	2.190
528	0.000162	0.140
529	0.005565	2.840
530	0.001200	0.530
531	0.000141	0.138

TABLE 5

Example Number	Mcl-1 HTRF IC_{50} (μM)	OPM-2 10% FBS IC_{50} IP (μM)
100001	0.000055	0.124
100002	0.000071	0.041
100003	0.00042	0.238
100004	0.000072	0.120
100005	0.000091	0.062
100006	0.000081	0.131
100007	0.000367	0.142
100008	0.000170	0.541
100009	0.000128	0.216
100010	0.000077	0.142
100011	0.000153	0.134
100012	0.000275	1.131
100013	0.000199	0.068
100014	0.000228	0.330
100015	0.001040	1.003
100016	0.000182	0.132
100017	0.000039	0.040
100018	0.000061	0.049
100019	0.000182	0.058

100020	0.000032	0.085
100021	0.001053	-
100022	0.000861	-
100023	0.003940	-
100024	0.006155	-
100025	0.002348	-
100026	0.002145	-
100027	0.007340	-
100028	0.001257	-
100029	0.008733	-
100030	0.010355	-
100031	0.007450	-
100032	0.000442	-
100033	0.002815	-
100034	0.000877	-
100035	0.000601	1.470
100036	0.000889	1.980
100037	0.001805	1.920
100038	0.001655	2.560
100039	0.000563	0.744
100040	0.002745	4.950

100041	0.003365	4.990
100042	0.004860	2.220
100043	0.001670	7.280
100044	0.031100	7.290
100045	0.000308	0.342
100046	0.003760	0.976
100047	0.005150	2.540
100048	0.000187	0.551
100049	0.001261	2.150
100050	0.001282	3.824
100051	0.000217	0.502
100052	0.000191	0.424
100053	0.000294	0.609
100054	0.004110	9.060
100055	0.001270	4.630
100056	0.000424	1.680
100057	0.000568	2.600
100058	0.001760	3.360
100059	0.011900	3.450
100060	0.004010	5.980
100061	0.000780	0.529

100062	0.004250	9.940
100063	0.002320	2.260
100064	0.002540	3.730
100065	0.004855	7.390
100066	0.001430	3.820
100067	0.001009	0.271
100068	0.004410	0.765
100069	0.000457	0.250
100070	0.004855	1.070
100071	0.001540	0.588
100072	0.000451	1.720
100073	0.000346	1.197
100074	0.000731	3.020
100075	0.000671	1.817
100076	0.009655	2.670
100077	0.000190	0.052
100078	0.000409	2.720
100079	0.000343	0.713
100080	0.000610	0.818
100081	0.007330	5.930
100082	0.000539	0.727

100083	0.000179	0.123
100084	0.000745	1.488
100085	0.000245	0.288
100086	0.000537	0.390
100087	0.000864	0.187
100088	0.002125	1.340
100089	0.000348	0.325
100090	0.000795	0.798
100091	0.001195	1.350
100092	0.004015	2.210
100093	0.000291	0.554
100094	0.003835	4.380
100095	0.000148	0.113
100096	0.000624	0.517
100097	0.000081	5.230
100098	0.000231	0.748
100099	0.000659	0.349
100100	0.002100	1.325
100101	0.000062	2.595
100102	0.000990	1.430
100103	0.000325	0.778

100104	0.000599	0.250
100105	0.005930	3.660
100106	0.000143	0.121
100107	0.000296	0.181
100108	0.000436	0.358
100109	0.000486	2.140
100110	0.001480	0.686
100111	0.000352	0.687
100112	0.001295	1.800
100113	0.000182	0.070
100114	0.001052	0.491
100115	0.004485	2.840
100116	0.003775	5.940
100117	0.002405	3.170
100118	0.004440	3.950
100119	0.001720	1.570
100120	0.000067	0.635
100121	0.000056	2.530
100122	0.000098	1.190
100123	0.000092	2.660
100124	0.000323	0.270

100125	0.000430	0.555
100126	0.000183	0.041
100127	0.000175	0.108
100128	0.000089	0.217
100129	0.002400	4.870
100130	0.002690	2.170
100131	0.000163	0.144
100132	0.000543	0.675
100133	0.000885	0.984
100134	0.000845	3.510
100135	0.000173	0.161
100136	0.000368	0.556
100137	0.000365	2.820
100138	0.000549	0.342
100139	0.002585	0.974
100140	0.000486	0.299
100141	0.001058	1.370
100142	0.000717	0.663
100143	0.001870	3.270
100144	-	0.208
100145	0.000357	0.945

100146	0.000515	0.347
100147	0.000305	0.666
100148	0.000113	0.239
100149	0.000214	0.186
100150	0.001685	1.430
100151	0.000120	0.071
100152	0.000449	0.377
100153	0.000738	4.660
100154	0.001720	1.070
100155	0.000225	0.332
100156	0.000410	0.568
100157	0.004810	3.210
100158	0.000298	0.260
100159	0.000559	0.591
100160	0.000169	0.078
100161	0.000355	0.757
100162	0.003470	2.870
100163	0.002790	1.000
100164	0.000917	0.967
100165	0.000455	0.579
100166	0.001765	0.945

100167	0.000377	0.339
100168	0.000249	0.196
100169	0.004825	2.270
100170	0.012100	7.820
100171	0.000578	0.868
100172	0.001295	1.570
100173	0.000539	0.379
100174	0.002025	1.910
100175	0.000149	0.452
100176	0.000480	0.603
100177	0.000258	0.259
100178	0.000432	0.237
100179	0.005810	0.840
100180	0.004917	4.425
100181	0.000537	0.226
100182	0.000863	0.827
100183	0.001340	2.245
100184	0.000717	0.179
100185	0.008883	5.130
100186	0.000377	0.312
100187	0.002760	3.110

100188	0.000877	0.735
100189	0.000820	0.701
100190	0.004790	2.480
100191	0.001600	0.557
100192	0.000192	0.149
100193	0.000856	1.300
100194	0.000613	0.619
100195	0.001075	0.625
100196	0.000461	0.358
100197	0.000774	2.460
100198	0.000307	0.399
100199	0.000166	0.148
100200	0.000213	1.070
100201	0.000086	0.307
100202	0.000352	0.928
100203	0.000285	0.491
100204	0.001655	5.270
100205	0.000206	0.068
100206	0.001260	1.750
100207	0.000141	0.215
100208	0.000431	0.318

100209	0.002675	3.380
100210	0.003475	3.360
100211	0.001435	4.780
100212	0.000901	1.620
100213	0.002845	2.020
100214	0.000143	0.095
100215	0.000595	1.250
100216	0.000311	0.374
100217	0.000183	0.130
100218	0.000621	0.675
100219	0.000401	0.974
100220	0.007415	6.840
100221	0.000525	0.776
100222	0.000182	0.222
100223	0.001410	2.150
100224	0.000345	0.385
100225	0.000639	0.882
100226	0.001395	0.849
100227	0.000423	0.191
100228	0.000558	3.300
100229	0.000356	1.490

100230	0.000473	0.544
100231	0.000312	0.350
100232	0.000152	0.389
100233	0.001040	0.257
100234	0.000237	0.449
100235	0.001345	0.644
100236	0.001096	0.933
100237	0.001740	0.996
100238	0.000474	0.747
100239	0.000333	3.740
100240	0.000385	0.266
100241	0.000365	0.401
100242	0.002145	1.450
100243	0.011500	8.670
100244	0.000182	0.049
100245	0.001715	1.980
100246	0.000326	0.114
100247	0.000542	0.624
100248	0.011050	6.680
100249	0.002995	2.270
100250	0.000136	0.082

100251	0.003290	3.730
100252	0.000112	0.077
100253	0.000149	0.544
100254	0.004070	2.150
100255	0.014450	5.020
100256	0.005040	1.200
100257	0.000180	0.080
100258	0.000553	0.519
100259	0.006180	1.250
100260	0.000408	0.094
100261	0.001220	0.533
100262	0.000134	0.433
100263	0.001830	3.390
100264	0.000384	0.600
100265	0.000439	0.441
100266	0.000292	0.571
100267	0.000166	0.274
100268	0.003440	3.810
100269	0.000908	1.230
100270	0.000776	3.72
100271	0.002480	6.120

100272	0.000401	0.349
100273	0.005655	8.660
100274	0.000377	0.543
100275	0.000113	0.309
100276	0.000326	1.528
100277	0.000266	0.448
100278	0.000458	0.333
100279	0.000777	3.25
100280	0.000368	0.305
100281	0.000117	0.352
100282	0.000268	1.280
100283	0.000143	0.806
100284	0.000285	0.396
100285	0.000241	0.642
100286	0.000471	1.580
100287	0.000494	1.870
100288	0.000103	0.089
100289	0.000878	3.960
100290	0.000116	0.259
100291	0.000137	0.281
100292	0.000115	0.672

100293	0.000522	0.726
100294	0.000118	0.116
100295	0.000279	0.302
100297	0.000115	0.168
100298	0.000140	0.199
100299	0.000350	0.623
100300	0.000109	0.235
100301	0.001315	1.930
100302	0.003805	4.880
100303	0.003640	7.330
100304	0.000311	0.464
100305	0.000473	1.140
100306	0.000124	0.278
100307	0.000049	1.030
100308	0.000033	1.170
100309	0.000244	0.385
100310	0.000152	0.120
100311	0.001030	1.190
100312	0.000088	0.234
100313	0.000129	0.143
100314	0.002925	2.290

100315	0.000200	0.153
100316	0.000276	0.375
100317	0.000188	0.157
100318	0.000095	0.114
100319	0.000126	0.506
100320	0.001200	2.140
100321	0.000209	0.285
100322	0.00223	1.54
100323	0.000477	1.250
100324	0.000244	1.170
100325	0.000182	0.482
100326	0.000615	0.334
100327	0.000295	0.550
100328	0.000261	0.180
100329	0.005023	1.560
100330	0.000083	8.260
100331	0.000192	8.260
100332	0.006465	4.31
100333	0.002100	2.170
100334	0.003273	1.470
100335	0.000319	0.165

100336	0.001123	1.810
100337	0.001608	2.410
100338	0.000502	1.920
100339	0.000186	1.380
100340	0.000779	0.308
100341	0.0041	1.94
100342	0.001685	0.782
100343	0.002510	0.617
100344	0.000309	0.290
100345	0.002420	0.218
100346	0.000735	0.248
100347	0.000689	1.080
100348	0.000135	0.125
100349	0.00115	0.058
100350	0.000489	0.554
100351	0.000115	2.02
100352	0.002750	0.246
100353	0.000348	0.151
100354	0.000109	0.147
100355	0.000535	0.776
100356	0.000084	0.071

100357	0.000224	0.399
100358	0.000118	0.081
100359	0.001200	1.540
100360	0.000848	1.230
100361	0.000208	0.155
100362	0.000888	2.1
100363	0.001383	3.810
100364	0.001160	1.680
100365	0.000257	0.245
100366	0.000198	0.168
100367	0.000371	0.604
100368	0.000377	0.611
100369	0.00283	9.92
100370	0.000153	0.258
100371	0.00039	0.307
100372	0.000165	0.833
100373	0.000318	0.736
100374	0.000289	0.433
100375	0.000070	0.176
100376	0.000150	0.362
100377	0.000107	0.182

100378	0.000037	0.111
100379	0.000060	0.071
100380	0.000208	0.137
100381	0.000328	2.910
100382	0.000471	0.312
100383	0.000264	3.430
100384	0.000821	0.729
100385	0.000144	0.144
100386	0.004017	7.27
100387	0.000175	3.760
100388	0.001167	2.160
100389	0.000101	0.114
100390	0.000186	0.649
100391	0.000441	0.282
100392	0.000112	0.129
100393	0.000164	0.211
100394	0.000242	0.622
100395	0.000056	0.040
100396	0.000272	1.470
100397	0.000198	0.404
100398	0.000618	0.457

100399	0.000280	2.810
100400	0.000838	1.320
100401	0.001797	8.390
100402	0.000098	0.133
100403	0.000226	0.39
100404	0.002553	8.15
100405	0.000545	1.120
100406	0.000360	0.747
100407	0.000278	0.516
100408	0.001353	5.62
100409	0.000124	0.206
100410	0.000127	0.297
100411	0.000584	2.1
100412	0.000097	0.249
100413	0.000228	0.556
100414	0.000626	1.270
100415	0.001950	2.285
100416	0.000092	0.086
100417	0.000345	0.379
100418	0.000098	0.141
100419	0.000277	0.416

100420	0.000112	0.161
100421	0.003926	4.93
100422	0.000174	0.182
100423	0.000056	0.099
100424	0.000249	0.469
100425	0.000165	0.717
100426	0.000197	0.110
100427	0.000209	0.342
100428	0.000210	0.218
100429	0.000176	1.420
100430	0.000057	0.358
100431	0.000043	0.290
100432	0.000228	0.711
100433	0.000026	0.296
100434	0.000162	0.482
100435	0.000055	0.305
100436	0.000076	0.335
100437	0.000073	0.531
100438	0.000169	0.547
100439	0.000619	2.640
100440	0.000398	0.354

100441	0.000133	0.154
100442	0.000921	3.870
100443	0.000070	0.156
100444	0.000098	0.646
100445	0.000040	0.098
100446	0.000126	0.345
100447	0.000050	0.184
100448	0.000373	1.920
100449	0.000071	0.171
100450	0.000336	1.910
100451	0.000111	0.412
100452	0.000077	0.157
100453	0.000927	2.930
100454	0.000652	0.802
100455	0.000087	0.140
100456	0.000565	1.230
100457	0.000331	0.967
100458	0.000210	0.418
100459	0.000685	0.732
100460	0.000095	0.433
100461	0.000042	0.382

100462	0.000304	0.652
100463	0.000383	1.130
100464	-	1.530
100465	0.000121	0.729
100466	0.000043	1.440
100467	0.000303	0.516
100468	0.000393	0.943
100469	0.000085	0.325
100470	0.000576	9.65
100471	0.000281	0.299
100472	0.000651	0.357
100473	0.000974	0.178
100474	0.000405	0.387
100475	0.001365	2.710
100476	-	1.340
100477	0.000313	0.159
100478	0.003470	4.090
100479	0.000758	0.332
100480	0.000176	0.221
100481	0.000094	0.152
100482	0.000183	0.105

100483	0.001664	1.690
100484	0.003850	3.370
100485	0.000192	0.272
100486	0.000381	0.102
100487	0.000436	0.340
100488	0.000389	0.346
100489	0.000880	0.182
100490	0.000292	0.511
100491	0.000208	0.308
100492	0.000749	0.436
100493	0.000322	0.512
100494	0.000078	0.089
100495	0.000462	0.539
100496	0.002665	5.060
100497	0.000064	0.106
100498	0.000885	1.660
100499	0.000509	1.120
100500	0.000049	0.071
100501	0.000090	0.518
100502	0.000290	0.393
100503	0.000493	0.706

100504	0.000803	1.890
100505	0.000165	0.137
100506	0.000497	1.270
100507	0.000430	0.490
100508	0.002734	2.500
100509	0.000057	0.361
100510	0.000070	0.379
100511	0.000070	0.430
100512	0.000415	1.490
100513	0.000071	0.288
100514	0.000088	0.231
100515	0.000132	0.585
100516	0.003360	1.900
100517	0.001059	3.460
100518	0.000427	0.668
100519	0.000175	0.138
100520	0.000549	1.690
100521	0.000197	0.296
100522	0.000144	0.538
100523	0.000812	0.622
100524	0.000990	0.842

100525	0.003305	1.430
100526	0.000387	0.826
100527	0.003595	3.570
100528	0.000138	0.257
100529	0.000287	0.245
100530	0.000171	0.448
100531	0.000083	0.172
100532	0.000053	8.637
100533	0.008565	3.990
100534	0.000799	0.542
100535	0.000570	0.964
100536	0.000204	0.826
100537	0.000115	0.256
100538	0.001470	2.400
100539	0.000144	0.727
100540	0.000275	0.320
100541	0.000760	0.826
100542	0.000229	0.902
100543	0.000451	0.821
100544	0.000171	0.306
100545	0.000153	0.231

100546	0.000084	0.440
100547	0.000031	1.860
100548	0.000064	8.410
100549	0.002570	0.545
100550	0.000059	6.859
100551	0.000174	0.142
100552	0.000065	0.957
100553	0.001040	2.790
100554	0.000231	0.519
100555	0.000101	0.113
100556	0.000113	0.734
100557	0.000093	0.299
100558	0.000086	0.274
100559	0.000113	1.030
100560	0.000041	2.020
100561	0.000275	0.673
100562	0.000057	0.532
100563	0.000065	0.510
100564	0.000333	1.430
100565	0.001540	2.060
100566	0.000142	0.590

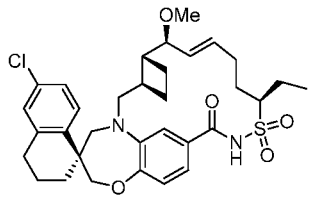
100567	0.000125	0.249
100568	0.000431	1.540
100569	0.002479	2.000
100570	0.003380	5.050
100571	0.000076	0.922
100572	0.000174	1.160
100573	0.002070	7.390
100574	0.001420	4.320
100575	0.001300	2.500
100576	0.001150	4.090
100577	0.000045	2.020
100578	0.000089	0.595
100579	0.000214	0.757
100580	0.000877	6.580
100581	0.000363	1.540
100582	0.000197	1.120
100583	0.000124	0.411
100584	0.000139	0.349
100585	0.000057	0.696
100586	0.000074	0.453
100587	0.000136	0.177

100588	0.000075	0.117
100589	0.001835	3.330
100590	0.000086	0.501
100591	0.000075	0.060
100592	0.000275	0.139
100593	0.000464	0.215
100594	0.000143	0.241
100595	0.000157	0.133
100596	0.000229	0.186
100597	0.000263	0.577
100598	0.000077	0.188
100599	0.001150	1.140
100600	0.000445	0.528
100601	0.000114	0.239
100602	0.000800	2.330
100603	0.000651	1.570
100604	0.000723	4.110
100605	0.003245	7.950
100606	0.000209	0.428

In-Vivo Data

Tumor Pharmacodynamics (PD)

Figures 1-7 illustrate the PD results of the cited Examples. The Reference Compound 1, an internal Amgen MCl-1 inhibitor compound made by one of the general schemes outlined in U.S. Patent No. 9,562,061, herein incorporated by reference, is (1S,3'R,6'R,7'S,8'E,12'R)-6-chloro-12'-ethyl-7'-methoxy-3,4-dihydro-2H,15'H-spiro[naphthalene-1,22'-[20]oxa[13]thia[1,14]diazatetracyclo[14.7.2.0~3,6~.0~19,24~]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide



Reference Compound 1

Female Athymic nude (Charles River Laboratories, Inc., Hollister CA) mice were inoculated subcutaneously with 5 x 10^6 OPM-2 Luc cells. When tumors reached 300-500 mm^3 in size, mice were randomized into treatment groups and harvested 6 hours post single dose of compound at various concentrations. Tumor lysates were analyzed for active Bak using a sandwich ELISA format (Active Bak MSD plate cat #N45ZA-1; Bak detection antibody Abcam Cat# Ab53153 and Sulfo-Tagged by MSD) and read on a MSD reader (S16000). Columns (n=3 per group) represent level of luminescence (cps). Statistical significance was determined by Oneway ANOVA followed by Dunnett's post hoc compared to the vehicle control group. Black diamonds represent drug plasma concentration and circles represent drug concentration in the tumor.

OPM-2 Xenograft

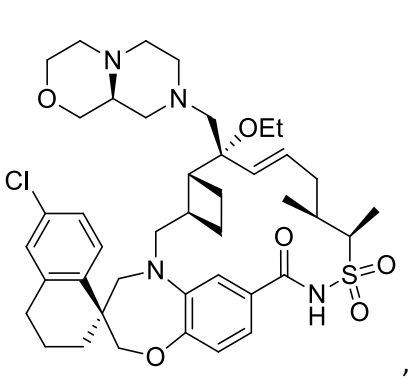
Examples 8-13 illustrate Xenograft data of various compounds of the present invention. Female Athymic nude (Charles River Laboratories, Inc., Hollister CA) mice were inoculated subcutaneously with 5 x 10^6 OPM-2 Luc cells. When average tumor volumes reached approximately 155-183 mm^3, animals were randomized (n=10/group) and dosed once daily by oral gavage (10-

12 days) with test compounds at various concentrations unless notes otherwise. Tumor volume and body weights were recorded twice per week using electronic calipers and an analytical scale. Statistical analysis was performed using Repeated Measures ANOVA (RMANOVA) followed by Dunnett's post-hoc analysis.

The foregoing description is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds, compositions and methods. Variations and changes, which are obvious to one skilled in the art, are intended to be within the scope and nature of the invention, as defined in the appended Claims. From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions. All patents and other publications recited herein are hereby incorporated by reference in their entireties.

Claims

1. A compound, wherein the compound is selected from:



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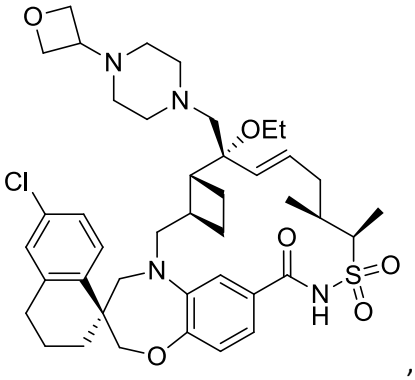

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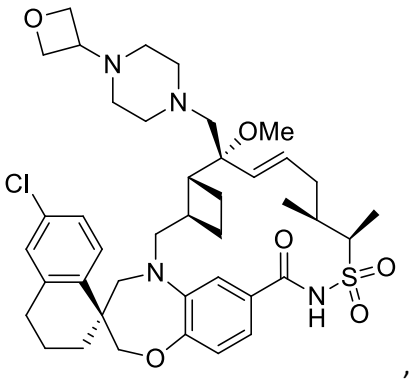

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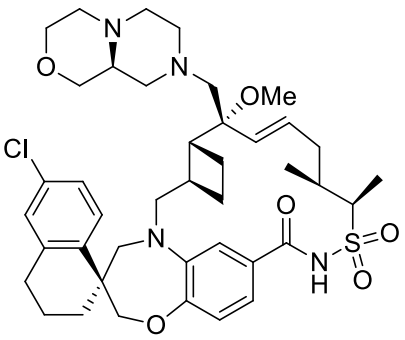

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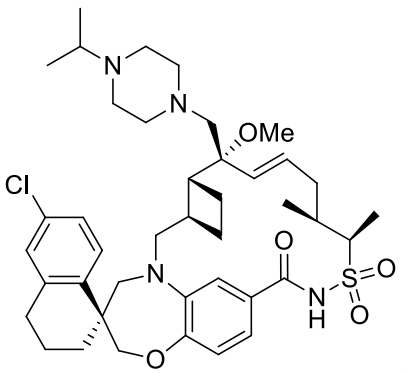

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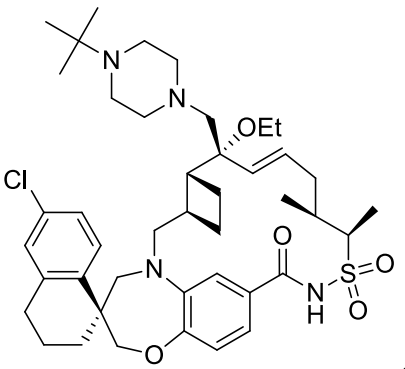

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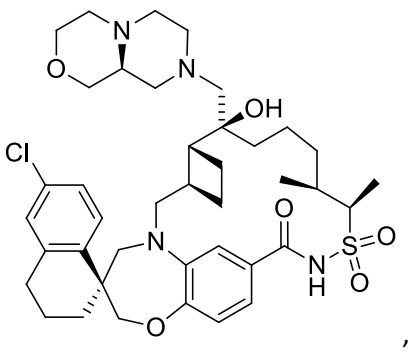

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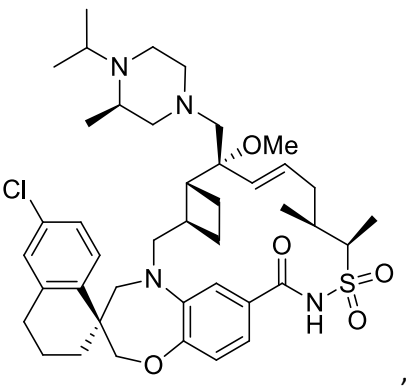

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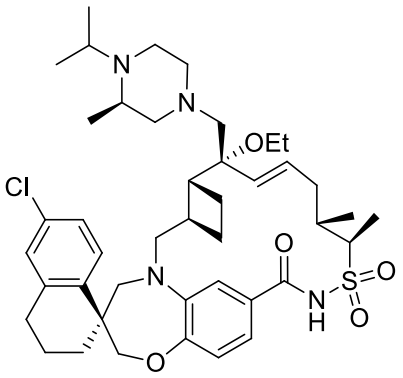
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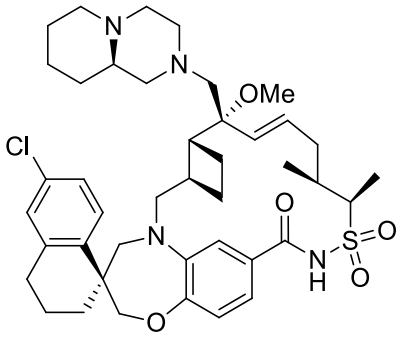
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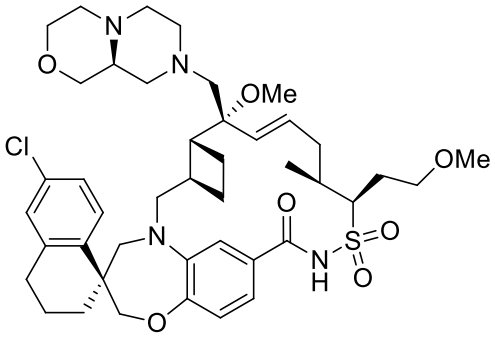
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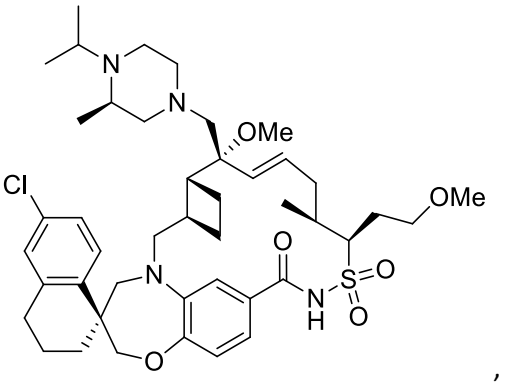
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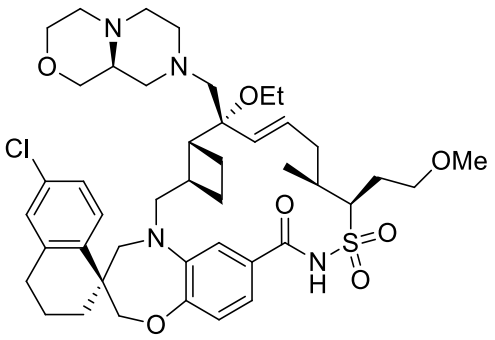
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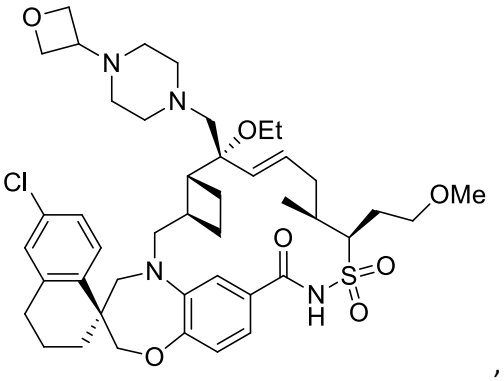
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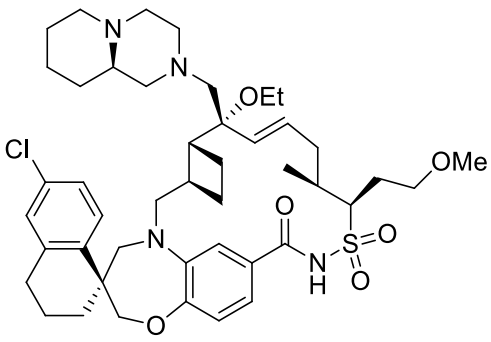
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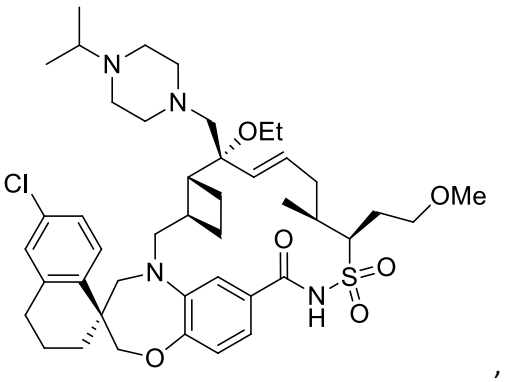
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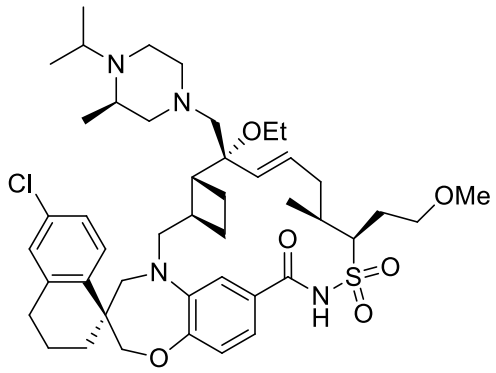
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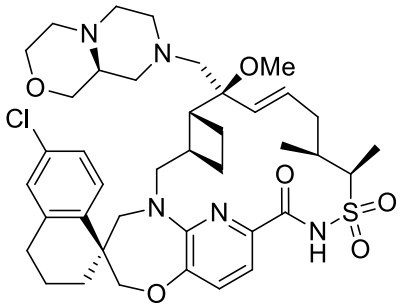
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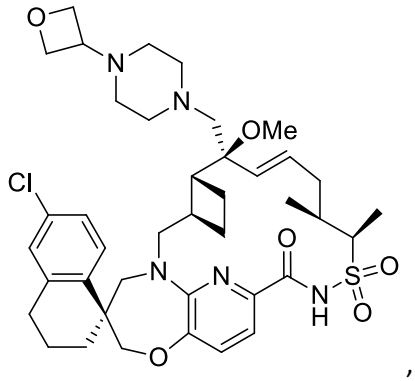
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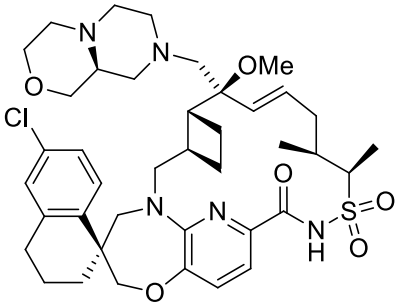
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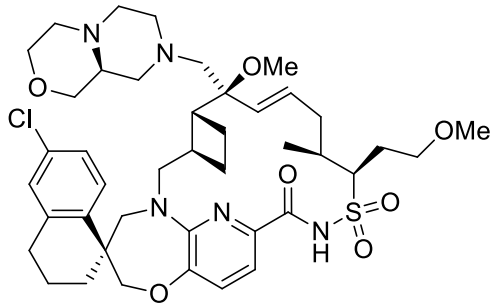
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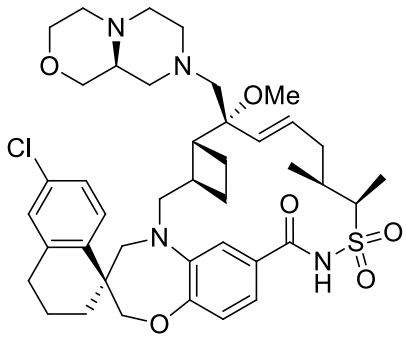
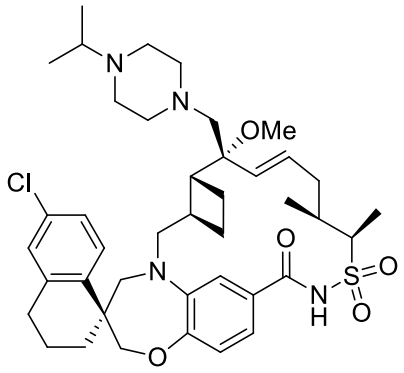
or the stereoisomer thereof, the pharmaceutically acceptable salt thereof, or the pharmaceutically acceptable salt of the stereoisomer thereof.

2. The compound of Claim 1 or the pharmaceutically acceptable salt thereof.

3. The compound of Claim 1, wherein the compound is

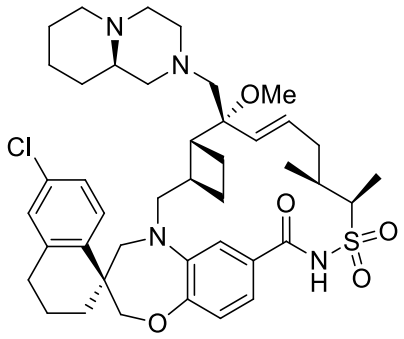

, or is the pharmaceutically acceptable salt thereof.

4. The compound of Claim 1, wherein the compound is



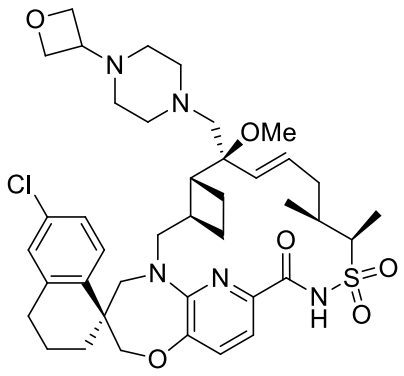
, or is the pharmaceutically acceptable salt thereof.

5. The compound of Claim 1, wherein the compound is



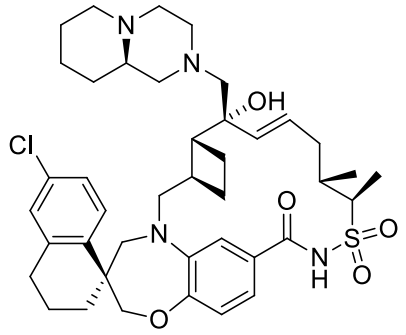
, or is the pharmaceutically acceptable salt thereof.

6. The compound of Claim 1, wherein the compound is



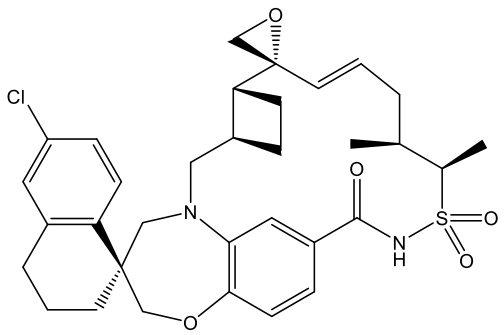
, or is the pharmaceutically acceptable salt thereof.

7. A compound, wherein the compound is



, or is the pharmaceutically acceptable salt thereof.

8. A compound, wherein the compound is



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9. A pharmaceutical composition comprising the compound of any one of Claims 1-7 or the pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

10. A pharmaceutical composition comprising the compound of Claim 3 or the pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

11. A pharmaceutical composition comprising the compound of Claim 4 or the pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

12. A pharmaceutical composition comprising the compound of Claim 5 or the pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

13. A pharmaceutical composition comprising the compound of Claim 6 or the pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

14. Use of a compound according to any one of Claims 1-7 in the preparation of a medicament for treating cancer.

15. The use according to Claim 14, wherein the cancer is a hematologic malignancy.

16. The use according to Claim 14, wherein the cancer is selected from the group consisting of breast cancer, colorectal cancer, skin cancer, melanoma, ovarian cancer, kidney cancer, lung cancer, non-small cell lung cancer, lymphoma, non-Hodgkin's lymphoma, myeloma, multiple myeloma, leukemia, and acute myelogenous leukemia.

17. The use according to Claim 14, wherein the cancer is multiple myeloma, acute myelogenous leukemia, or non-Hodgkin's lymphoma.