HYGROMYCIN DERIVATIVES

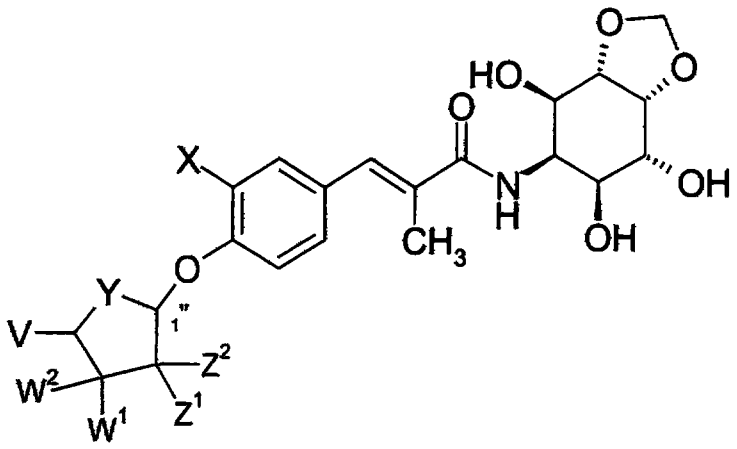
Background Of The Invention

This invention relates to novel hygromycin derivatives that are useful as antibacterial and antiprotozoal agents in mammals, including man, as well as in fish and birds. This invention also relates to pharmaceutical compositions containing the novel compounds and to methods of treating bacterial and protozoal infections in mammals, fish and birds by administering the novel compounds to mammals, fish and birds requiring such treatment.

Hygromycin A is a fermentation-derived natural product first isolated from *Streptomyces hygroscopicus* in 1953. As an antibiotic, hygromycin A possesses activity against human pathogens and is reported to possess potent *in vitro* activity against *Serpulina (Treponema) hyodysenteriae* which causes swine dysentery. Several references refer to semisynthetic modifications of hygromycin A, including the following: derivatization of the 5" ketone of hygromycin A to the 2,4-dinitrophenylhydrazone is referred to in K. Isono *et al.*, *J. Antibiotics* **1957**, 10, 21, and R.L. Mann and D.O. Woolf, *J. Amer Chem. Soc.* **1957**, 79, 120. K. Isono *et al.*, ibid., also refer to the thiosemicarbazone at 5"; reduction of the 5" ketone of hygromycin A to the 5" alcohol is referred to in R.L. Mann and D.O. Woolf, ibid., as well as in S.J. Hecker *et al.*, *Bioorg. Med. Chem. Lett.* **1992**, 2, 533 and S.J. Hecker *et al.*, *Bioorg. Med. Chem. Lett.* **1993**, 3, 295; furanose analogues are referred to in B.H. Jaynes et al., *Bioorg. Med. Chem. Lett.* **1993**, 3, 1531, and B.H. Jaynes et al., *J. Antibiot.* **1992**, 45, 1705; aromatic ring analogues are referred to in S.J. Hecker et al., *Bioorg. Med. Chem. Lett.* **1993**, 3, 289, and C.B. Cooper et al., *Bioorg. Med. Chem. Lett.* **1997**, 7, 1747; enamide analogues are referred to in S.J. Hecker et al., *Bioorg. Med. Chem. Lett.* **1992**, 2, 533; aminocyclitol analogues are referred to in S.J. Hecker et al., *Bioorg. Med. Chem. Lett.* **1992**, 2, 1015, and in S.J. Hecker et al., *Bioorg. Med. Chem. Lett.* **1992**, 2, 1043. The hygromycin A derivatives of the present invention possess broad activity against both gram-negative and gram-positive bacteria and protozoa. WO 99/012941, published September 14, 1999, refers to the treatment of bacterial infections by co-adminstering hygromycin and/or epihygromycin with a pyridone carboxylic acid antibacterial compound such as tosufloxacin, nalidixic acid, piromidic acid cinoxacin and/or enoxacin. Hygromycin derivatives are also described and claimed in United States provisional patent application number 60/110,618 (filed December 2, 1998), United States patent application number 09/380,718 (filed April 8, 1999), and PCT international patent application number PCT/IB99/00795 (filed May 13, 1999). The foregoing United States and PCT applications are incorporated herein by reference in their entirety.

Summary of the Invention

The present invention relates to compounds of the formula



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or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

X is H, F, OH, or NH_2;

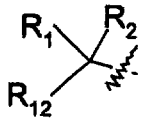
Y is O or CH_2;

Z^1 is R^3 and Z^2 is OR^{13}; or Z^1 is H and Z^2 is R^3, $-NR^3R^4$, $-NR^3C(O)R^4$, or F;

or Z^1 and Z^2 are taken together to form =O or $=NOR^3$;

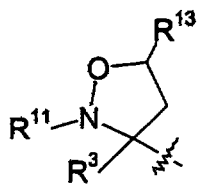
W^1 is R^3 and W^2 is OR^{13}; or W^1 is H and W^2 is R^3, $-NR^3R^4$, $-NR^3C(O)R^4$, or F;

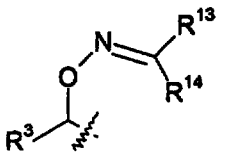
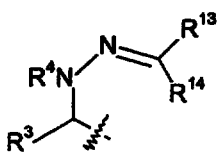
or W^1 and W^2 are taken together to form =O or $=NOR^3$;

V is a group having the following structure 

or V is $R^3OC(O)$-, $R^3R^4NC(O)$- or $R^3O(R^4)NC(O)$-, in which groups R^3 and R^4 optionally can be taken together to form a 4 to 10 membered heterocyclic group which may be optionally substituted by 1 to 3 R^6 groups;

or V is a group having the following structure:



or V is a group of the structure  or , where both E and Z isomers are included;

or V is a carbon-linked 4 to 10 membered heterocyclic group, which may be optionally substituted by 1 to 3 R^6 groups;

R^1 is H and R^2 is $-NR^3R^4$, $-NR^4C(O)R^3$, $-OC(O)NR^3R^4$ or $-OR^3$;

or R^1 and R^2 are taken together to form O, =N-OR^3, or $=C(R^5)X^1-X^2-R^8$, wherein:

X^1 is $-CR^9R^{10}-$, and X^2 is selected from $-CR^9R^{10}-$, $-S(O)_n-$ wherein n is an integer from 0 to 2, $-NR^9-$, and O; where X^2 is $-NR^9-$, then R^8 and R^9 may be taken together to form a 5 to 12 membered heterocyclic group, which is optionally substituted by 1 to 3 R^6 groups; or X^1 and X^2 independently or together represent a bond with the proviso that if X^1 is a bond than X^2 is either a bond or $-CR^9R^{10}-$;

each R^3 is independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(CR^9R^{10})_t(C_3$-C_{10} cycloalkyl), $-(CR^9R^{10})_t(C_6$-C_{10} aryl), and $-(CR^9R^{10})_t$(4 to 10 membered heterocyclic), wherein each t is independently an integer from 0 to 5, said alkyl, alkenyl and alkynyl groups optionally contain 1 or 2 hetero moieties selected from O, $-S(O)_j-$ wherein j is an integer from 0 to 2, and $-N(R^9)-$ with the proviso that two O atoms, two S atoms, or an O and S atom are not attached directly to each other, and the proviso that an O atom, a S atom or a N atom are not attached directly to a triple bond or non-aromatic double bond; said cycloalkyl, aryl and heterocyclic R^3 groups are optionally fused to a benzene ring, a C_5-C_8 cycloalkyl group, or a 4 to 10 membered heterocyclic group; the $-(CR^9R^{10})_t-$ moieties of the foregoing R^3 groups optionally include a carbon-carbon double or triple bond where t is an integer between 2 and 5; and the foregoing R^3 groups, except H but including any optional fused rings referred to above, are optionally substituted by 1 to 5 R^6 groups, and with the proviso that R^3 must be attached through a carbon atom unless R^3 is H;

each R^4 is independently H or C_1-C_{10} alkyl;

R^5 is H or C_1-C_6 alkyl, wherein the foregoing R^5 alkyl group is optionally substituted by 1 or 2 R^6 groups

each R^6 is independently selected from C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, oxo, halo, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-OR^7$, $-C(O)R^7$, $-C(O)OR^7$, $-NR^9C(O)OR^{11}$, $-OC(O)R^7$, $-NR^9SO_2R^{11}$, $-SO_2NR^7R^8$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, $-NR^7R^9$, $-S(O)_j(CR^9R^{10})_m(C_6$-$C_{10}$ aryl), $-S(O)_j(C_1$-C_6 alkyl), wherein j is an integer from 0 to 2, $-(CR^9R^{10})_m(C_6$-C_{10} aryl), $-O(CR^9R^{10})_m(C_6$-C_{10} aryl), $-NR^9(CR^9R^{10})_m(C_6$-

integer from 0 to 4; said alkyl, alkenyl and alkynyl groups optionally contain 1 or 2 hetero moieties selected from O, $-S(O)_j-$ wherein j is an integer from 0 to 2, and $-N(R^7)-$ with the proviso that two O atoms, two S atoms, or an O and S atom are not attached directly to each other, and the proviso that an O atom, a S atom or a N atom are not attached directly to a triple bond or a non-aromatic double bond; said cycloalkyl, aryl and heterocyclic R^6 groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 cycloalkyl group, or a 4 to 10 membered heterocyclic group; and said alkyl, cycloalkyl, aryl and heterocyclic R^6 groups are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-NR^9SO_2R^{11}$, $-SO_2NR^7R^9$, $-C(O)R^7$, $-C(O)OR^7$, $-OC(O)R^7$, $-NR^9C(O)OR^{11}$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, $-NR^7R^9$, $-OR^7$, C_1-C_{10} alkyl, $-(CR^9R^{10})_m(C_6$-C_{10} aryl), and $-(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 4;

each R^7 is independently selected from H, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, $-(CR^9R^{10})_m(C_6$-C_{10} aryl), and $-(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer from 0 to 4; said alkyl group optionally includes 1 or 2 hetero moieties selected from O, $-S(O)_j-$ wherein j is an integer ranging from 0 to 2, and $-N(R^9)-$ with the proviso that two O atoms, two S atoms, or an O and S atom are not attached directly to each other; said cycloalkyl, aryl and heterocyclic R^7 groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 cycloalkyl group, or a 4 to 10 membered heterocyclic group; and the foregoing R^7 substituents, except H, are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-C(O)R^9$, $-C(O)OR^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)NR^9R^{10}$, $-NR^9R^{10}$, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy, and with the proviso that R^7 must be attached through a carbon atom unless R^7 is H;

each R^8 is independently selected from R^3, $-C(O)R^3$, or $-C(O)NR^9R^3$, wherein R^3 is as defined above;

each R^9 and R^{10} is independently H or C_1-C_6 alkyl; and,

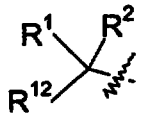
R^{11} is selected from the substituents provided in the definition of R^7 except H.

R^{12} is selected from the substituents provided in the definition of R^3, except that R^{12} cannot be methyl if (a) X is OH, Y is O, W^1 is H, W^2 is α-OH, Z^1 is H, Z^2 is β-OH; or (b) if X is OH, Y is O, W^1 is H, W^2 is α-OH, Z^1 and Z^2 are both H; and with the proviso that R^{12} must be attached through a carbon atom unless R^{12} is H;

R^{13} is defined as described for R^3; and,

R^{14} is H or C_1 –C_{10} alkyl, except that R^{14} cannot be H when R^{13} is H.

In a first preferred embodiment of the compound of formula 1:

V equals  and the preferred configuration of the 1" center is that of hygromycin A

In a second preferred embodiment of the compound of formula 1:

V is as indicated in the first preferred embodiment above, but R^1 and R^2 are taken together as =O or =NOR^3.

In a third preferred embodiment of the compound of formula 1:

the preferred groups as indicated for the second preferred embodiment, but:

Z^1 is R^3 and Z^2 is OR^{13}; or Z^1 is H and Z^2 is R^3, $-NR^3R^4$, $-NR^3C(O)R^4$, or F; and W^1 is R^3 and W^2 is OR^{13}; or W^1 is H and W^2 is R^3, $-NR^3R^4$, $-NR^3C(O)R^4$, or F; wherein each R^3 and R^{13} are independently selected from H, C_1-C_4 alkyl, $-(CR^9R^{10})_t(C_3$-C_{10} cycloalkyl), $-(CR^9R^{10})_t(C_6$-C_{10} aryl), and $-(CR^9R^{10})_t$(4 to 10 membered heterocyclic), wherein each t is independently an integer from 0 to 3, said alkyl group optionally contains 1 hetero moiety selected from O, $-S(O)_j-$ wherein j is an integer from 0 to 2, and $-N(R^9)-$, and the foregoing R^3 and R^{13} groups, except H, are optionally substituted by 1 to 5 R^6 groups, and with the proviso that R^3 and R^{13} must be attached through a carbon atom unless it is H; each R^4 is independently H or C_1-C_4 alkyl; each R^6 is independently selected from C_1-C_4 alkyl, oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-OR^7$, $-C(O)R^7$, $-NR^9C(O)OR^{11}$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, $-NR^7R^9$; wherein R^7 and R^9 are H, C_1-C_4 alkyl; R^{11} is C_1-C_4 alkyl.

R^1 and R^2 are taken together as =O or =NOR^3, wherein each R^3 is independently selected from C_1-C_4 alkyl, C_3-C_8 alkenyl, $-(CR^9R^{10})_t(C_6$-C_{10} aryl), and $-(CR^9R^{10})_t$(4 to 10 membered heterocyclic), wherein each t is independently an integer ranging from 0 to 3, said alkyl and alkenyl groups optionally contain 1 or 2 hetero moieties selected from O, $-S(O)_j-$ wherein j is an integer ranging from 0 to 2 and $-N(R^9)-$, with the proviso that two O atoms, two S atoms, or an O and S atom are not attached directly to each other, and the proviso that an O atom, a S atom or a N atom are not attached directly to a non-aromatic double bond; said aryl and heterocyclic R^3 groups are optionally fused to a benzene ring, a C_5-C_8 cycloalkyl group, or a 4 to 10 membered heterocyclic group; and the foregoing R^3 groups, including any optional fused rings referred to above, are optionally substituted by 1 to 5 R^6 groups, and with the proviso that R^3 must be attached through a carbon atom; R^{12} is C_1-C_4 alkyl, and said alkyl group is optionally substituted by 1 to 3 R^6 groups, except that R^{12} cannot be methyl if (a) X is OH, Y is O, W^1 is H, W^2 is α-OH, Z^1 is H, Z^2 is β-OH, or if (b) X is OH, Y is O, W^1 is H, W^2 is α-OH, Z^1 is H, Z^2 is H; each R^6 is independently selected from C_1-C_4 alkyl, oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-OR^7$, $-C(O)R^7$, $-NR^9C(O)OR^{11}$, $-NR^9SO_2R^{11}$, $-SO_2NR^7R^9$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, $-NR^7R^9$, $-S(O)_j(CR^9R^{10})_m(C_6$-$C_{10}$ aryl), $-S(O)_j(C_1$-C_6

alkyl), wherein j is an integer ranging from 0 to 2, -$(CR^9R^{10})_m(C_6$-C_{10} aryl), -$O(CR^9R^{10})_m(C_6$-C_{10} aryl), -$NR^9(CR^9R^{10})_m(C_6$-C_{10} aryl), and -$(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer from 0 to 2; and said alkyl, cycloalkyl, aryl and heterocyclic R^6 groups are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, -$NR^9SO_2R^{11}$, -$C(O)R^7$, -$NR^9C(O)OR^{11}$, -$NR^9C(O)R^7$, -$C(O)NR^7R^9$, -NR^7R^9, -OR^7, C_1-C_4 alkyl, -$(CR^9R^{10})_m(C_6$-C_{10} aryl), and -$(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer from 0 to 2; R^7 is independently selected from H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, -$(CR^9R^{10})_m(C_6$-C_{10} aryl), and -$(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer from 0 to 2; said alkyl group optionally includes 1 hetero moiety selected from O, -$S(O)_j$- wherein j is an integer from 0 to 2, and -$N(R^9)$-; said cycloalkyl, aryl and heterocyclic R^7 groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 cycloalkyl group, or a 4 to 10 membered heterocyclic group; and the foregoing R^7 substituents, except H, are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, -$C(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)NR^9R^{10}$, -NR^9R^{10}, hydroxy, C_1-C_4 alkyl, and C_1-C_4 alkoxy, and with the proviso that R^7 must be attached through a carbon atom unless R^7 is H; R^9 and R^{10} are independently H, C_1-C_4 alkyl; R^{11} is selected from R^7 except H.

In a fourth preferred embodiment of the compound of formula 1:

the preferred groups as indicated for the third preferred embodiment, but:

X is F, H or OH;

Y is O;

W^1 is R^3, W^2 is OR^{13}; or W^1 is H, W^2 is R^3 or F; Z^1 is R^3, Z^2 is OR^{13}; or Z^1 is H, Z^2 is R^3 or F; wherein R^3 and R^{13} are independently H, C_1-C_4 alkyl, and said alkyl groups are optionally substituted by 1 to 3 R^6 groups; wherein each R^6 is independently oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, -OR^7, -$C(O)R^7$, -$NR^9C(O)OR^{11}$, -$NR^9C(O)R^7$, -$C(O)NR^7R^9$, or -NR^7R^9; wherein R^7 and R^9 are H or C_1-C_4 alkyl; R^{11} is C_1-C_4 alkyl;

R^1 and R^2 are taken together as =NOR^3, R^3 is -$(CR^9R^{10})_t(C_6$-C_{10} aryl), and -$(CR^9R^{10})_t$(4 to 10 membered heterocyclic), wherein each t is independently an integer from 0 to 3; the foregoing R^3 groups are optionally substituted by 1 to 5 R^6 groups, and with the proviso that R^3 must be attached through a carbon atom; R^{12} is C_1-C_4 alkyl, and said alkyl group is optionally substituted by 1 to 3 R^6 groups, except that R^{12} cannot be methyl if (a) X is OH, Y is O, W^1 is H, W^2 is α-OH, Z^1 is H, Z^2 is β-OH, or if (b) X is OH, Y is O, W^1 is H, W^2 is α-OH, Z^1 is H, Z^2 is H; wherein R^6 is C_1-C_4 alkyl, oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, -OR^7, -$C(O)R^7$, -$NR^9C(O)OR^{11}$, -$NR^9C(O)R^7$, -$C(O)NR^7R^9$, -NR^7R^9, -$(CR^9R^{10})_m(C_6$-C_{10} aryl), -$O(CR^9R^{10})_m(C_6$-C_{10} aryl), -$NR^9(CR^9R^{10})_m(C_6$-C_{10} aryl), and

$-(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer from 0 to 2; said alkyl, aryl and heterocyclic R^6 groups are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-NR^9SO_2R^{11}$, $-C(O)R^7$, $-NR^9C(O)OR^{11}$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, $-NR^7R^9$, $-OR^7$, and C_1-C_4 alkyl;

R^7 is independently selected from H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, $-(CR^9R^{10})_m$(C_6-C_{10} aryl), and $-(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 2; the foregoing R^7 substituents, except H, are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-C(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)NR^9R^{10}$, $-NR^9R^{10}$, hydroxy, C_1-C_4 alkyl, and C_1-C_4 alkoxy; each R^9 and R^{10} are independently H or C_1-C_4 alkyl; R^{11} is selected from R^7 except H.

In a fifth preferred embodiment of the compound of formula 1:

the preferred groups as indicated for the fourth preferred embodiment, but:

Z^1 is H, Z^2 is OH; or Z^1 is methyl, Z^2 is OH; or both Z^1 and Z^2 are H; or Z^1 is H, Z^2 is F;

W^1 is H, W^2 is OH;

R^1 and R^2 are taken together as $=NOR^3$, wherein R^3 is $-(CR^9R^{10})_t$(C_6-C_{10} aryl), and $-(CR^9R^{10})_t$(4 to 10 membered heterocyclic), wherein each t is independently an integer ranging from 0 to 2, and the foregoing R^3 groups are optionally substituted by 1 to 5 R^6 groups; wherein R^6 is C_1-C_4 alkyl, oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-OR^7$, $-C(O)R^7$, $-(CR^9R^{10})_m$(C_6-C_{10} aryl), $-O(CR^9R^{10})_m$(C_6-C_{10} aryl), and $-(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 2; said alkyl, aryl and heterocyclic R^6 groups are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-C(O)R^7$, $-NR^9C(O)OR^{11}$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, $-OR^7$, and C_1-C_4 alkyl;

R^7 is independently selected from H, C_1-C_4 alkyl; the foregoing R^7 substituents, except H, are optionally substituted by 1 to 3 substituents independently selected from trifluoromethyl, $-C(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)NR^9R^{10}$, $-NR^9R^{10}$, hydroxy, and C_1-C_4 alkoxy; R^9 and R^{10} are independently H, C_1-C_4 alkyl; R^{11} is selected from R^7 except H; R^{12} is C_1-C_4 alkyl except that R^{12} cannot be methyl if (a) X is OH, Y is O, W^1 is H, W^2 is α-OH, Z^1 is H, Z^2 is β-OH, or if (b) X is OH, Y is O, W^1 is H, W^2 is α-OH, Z^1 is H, Z^2 is H.

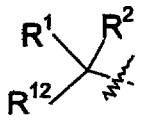
In a sixth preferred embodiment of the compound of formula 1:

the preferred groups as indicated for the fifth preferred embodiment, but:

R^1 and R^2 are taken together as $=NOR^3$, wherein R^3 is $-(CR^9R^{10})_t$-phenyl, and $-(CR^9R^{10})_t$(5 to 9 membered heterocyclic), where t is 0 or 1, and the foregoing R^3 groups are optionally substituted by 1 to 5 R^6 groups, wherein each R^6 is independently C_1-C_4 alkyl, halo,

trifluoromethyl, and -$(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer from 0 to 1; said heterocyclic R^6 groups are optionally substituted by 1 to 5 substituents independently selected from halo, trifluoromethyl, and C_1-C_4 alkyl; each R^9 and R^{10} is independently H or C_1–C_3 alkyl.

In a seventh preferred embodiment of the compound of formula 1:

V equals 

and R^1 and R^2 are taken together as =$C(R^5)X^1$-X^2-R^8 and the preferred configuration of the 1" center is that of hygromycin A

In an eighth preferred embodiment of the compound of formula 1:

the preferred groups as indicated for the seventh preferred embodiment, but:

W^1 is R^3, W^2 is OR^{13}; or W^1 is H, W^2 is R^3, NR^3R^4, $NR^3C(O)R^4$, or F; Z^1 is R^3, Z^2 is OR^{13}; or Z^1 is H, Z^2 is R^3, NR^3R^4, $NR^3C(O)R^4$, or F; wherein R^3 and R^{13} are independently selected from H, C_1-C_4 alkyl, -$(CR^9R^{10})_t$(C_3-C_{10} cycloalkyl), -(C R^9R10)$_t$(C_6-C_{10} aryl), and -$(CR^9R^{10})_t$(4 to 10 membered heterocyclic), wherein each t is independently an integer ranging from 0 to 3, said alkyl group optionally contains 1 hetero moiety selected from O, -$S(O)_j$- wherein j is an integer ranging from 0 to 2, and -$N(R^9)$-, and the foregoing R^3 and R^{13} groups, except H, are optionally substituted by 1 to 5 R^6 groups, and with the proviso that R^3 and R^{13} must be attached through a carbon atom unless it is H; each R^4 is independently H or C_1-C_4 alkyl; each R^6 is independently selected from C_1-C_4 alkyl, oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, -OR^7, -$C(O)R^7$, -$NR^9C(O)OR^{11}$, -$NR^9C(O)R^7$, -$C(O)NR^7R^9$, and -NR^7R^9; wherein each R^7 and R^9 is independently H or C_1-C_4 alkyl; R^{11} is C_1-C_4 alkyl;

R^1 and R^2 are taken together as =$C(R^5)X^1$-X^2-R^8; wherein X^1 is –CR^9R^{10}-, and X^2 is selected from –CR^9R^{10}-, -$S(O)_n$- wherein n is 0 to 2, -NR^9-, and O; where X^2 is –NR^9-, then R^8 and R^9 may be taken together to form a 5 to 12 membered heterocyclic, which is optionally substituted by 1 to 3 R^6 groups; X^1 and X^2 can also independently or together represent a bond with the proviso that if X^1 is a bond than X^2 must be either a bond or –CR^9R^{10}-;

and where R^5 is H or C_1-C_6 alkyl, wherein the foregoing R^5 alkyl group is optionally substituted by 1 or 2 R^6 groups:

and where each R^8 is independently selected from R^3, -$C(O)R^3$, or -$C(O)NR^9R^3$, with the additional proviso that an N and O atom, and an N and S atom are not attached directly to each other, wherein each R^3 is independently selected from C_1-C_4 alkyl, C_3-C_8 alkenyl, -$(CR^9R^{10})_t$(C_6-C_{10} aryl), and -$(CR^9R^{10})_t$(4 to 10 membered heterocyclic), wherein each t is independently an integer ranging from 0 to 3, said alkyl or alkenyl group optionally contains 1 hetero moiety selected from O, -$S(O)_j$- wherein j is an integer ranging from 0 to 2, and -$N(R^9)$-,

with the proviso that an O atom, a S atom or a N atom are not attached directly to a non-aromatic double bond; said aryl and heterocyclic R^3 groups are optionally fused to a benzene ring, a C_5-C_8 cycloalkyl group, or a 4 to 10 membered heterocyclic group; and the foregoing R^3 groups, including any optional fused rings referred to above, are optionally substituted by 1 to 5 R^6 groups, and with the proviso that R^3 must be attached through a carbon atom; R^{12} is C_1-C_4 alkyl, and said alkyl group is optionally substituted by 1 to 3 R^6 groups, except that R^{12} cannot be methyl if (a) X is OH, Y is O, W^1 is H, W^2 is α-OH, Z^1 is H, Z^2 is β-OH, or if (b) X is OH, Y is O, W^1 is H, W^2 is α-OH, Z^1 is H, Z^2 is H; each R^6 is independently selected from C_1-C_4 alkyl, oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-OR^7$, $-C(O)R^7$, $-NR^9C(O)OR^{11}$, $-NR^9SO_2R^{11}$, $-SO_2NR^7R^9$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, $-NR^7R^9$, $-S(O)_j(CR^9R^{10})_m$(C_6-C_{10} aryl), $-S(O)_j$(C_1-C_6 alkyl), wherein j is an integer ranging from 0 to 2, $-(CR^9R^{10})_m$(C_6-C_{10} aryl), $-O(CR^9R^{10})_m$(C_6-C_{10} aryl), $-NR^9(CR^9R^{10})_m$(C_6-C_{10} aryl), and $-(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 2; and said alkyl, cycloalkyl, aryl and heterocyclic R^6 groups are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-NR^9SO_2R^{11}$, $-C(O)R^7$, $-NR^9C(O)OR^{11}$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, $-NR^7R^9$, $-OR^7$, C_1-C_4 alkyl, $-(CR^9R^{10})_m$(C_6-C_{10} aryl), and $-(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 2; R^7 is independently selected from H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, $-(CR^9R^{10})_m$(C_6-C_{10} aryl), and $-(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 2; said alkyl group optionally includes 1 hetero moiety selected from O, $-S(O)_j$- wherein j is an integer ranging from 0 to 2, and $-N(R^9)$-; said cycloalkyl, aryl and heterocyclic R^7 groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 cycloalkyl group, or a 4 to 10 membered heterocyclic group; and the foregoing R^7 substituents, except H, are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-C(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)NR^9R^{10}$, $-NR^9R^{10}$, hydroxy, C_1-C_4 alkyl, and C_1-C_4 alkoxy, and with the proviso that R^7 must be attached through a carbon atom unless R^7 is H; each R^9 and R^{10} are independently H or C_1-C_4 alkyl; R^{11} is selected from R^7 except H.

In a ninth preferred embodiment of the compound of formula **1**:

the preferred groups as indicated for the eighth preferred embodiment, but:

X is F, H or OH;

Y is O;

W^1 is R^3, W^2 is OR^{13}; or W^1 is H, W^2 is R^3, NR^3R^4, or F; Z^1 is R^3, Z^2 is OR^{13}; or Z^1 is H, Z^2 is R^3, NR^3R^4, or F; wherein each R^3 and R^{13} are independently H or C_1-C_4 alkyl, and said alkyl groups are optionally substituted by 1 to 3 R^6 groups; wherein each R^6 is independently

oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, -OR^7, -$C(O)R^7$, -$NR^9C(O)OR^{11}$, -$NR^9C(O)R^7$, -$C(O)NR^7R^9$, and -NR^7R^9; wherein each R^7 and R^9 is independently H or C_1-C_4 alkyl; R^{11} is C_1-C_4 alkyl;

R^1 and R^2 are taken together as =$C(R^5)X^1$-X^2-R^8; wherein X^1 is –CR^9R^{10}-, and X^2 is selected from –CR^9R^{10}-, -$S(O)_n$- wherein n is 0 to 2, -NR^9-, and O; where X^2 is –NR^9-, then R^8 and R^9 may be taken together to form a 5 to 12 membered heterocyclic, which is optionally substituted by 1 to 3 R^6 groups; X^1 and X^2 can also independently or together represent a bond with the proviso that if X^1 is a bond than X^2 must be either a bond or –CR^9R^{10}-;

and where R^5 is H or C_1-C_6 alkyl, wherein the foregoing R^5 alkyl group is optionally substituted by 1 or 2 R^6 groups;

and where R^8 is R^3 wherein each R^3 is independently -$(CR^9R^{10})_t$(C_6-C_{10} aryl) or -$(CR^9R^{10})_t$(4 to 10 membered heterocyclic), wherein each t is independently an integer ranging from 0 to 3; the foregoing R^3 groups are optionally substituted by 1 to 5 R^6 groups, and with the proviso that R^3 must be attached through a carbon atom; R^{12} is C_1-C_4 alkyl, and said alkyl group is optionally substituted by 1 to 3 R^6 groups, except that R^{12} cannot be methyl if (a) X is OH, Y is O, W^1 is H, W^2 is α-OH, Z^1 is H, Z^2 is β-OH, or if (b) X is OH, Y is O, W^1 is H, W^2 is α-OH, Z^1 is H, Z^2 is H; wherein each R^6 is independently C_1-C_4 alkyl, oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, -OR^7, -$C(O)R^7$, -$NR^9C(O)OR^{11}$, -$NR^9C(O)R^7$, -$C(O)NR^7R^9$, -NR^7R^9, -$(CR^9R^{10})_m$(C_6-C_{10} aryl), -$O(CR^9R^{10})_m$(C_6-C_{10} aryl), -$NR^9(CR^9R^{10})_m$(C_6-C_{10} aryl), and -$(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 2; said alkyl, aryl and heterocyclic R^6 groups are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, -$NR^9SO_2R^{11}$, -$C(O)R^7$, -$NR^9C(O)OR^{11}$, -$NR^9C(O)R^7$, -$C(O)NR^7R^9$, -NR^7R^9, -OR^7, and C_1-C_4 alkyl;

each R^7 is independently selected from H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, -$(CR^9R^{10})_m$(C_6-C_{10} aryl), and -$(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 2; the foregoing R^7 substituents, except H, are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, -$C(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)NR^9R^{10}$, -NR^9R^{10}, hydroxy, C_1-C_4 alkyl, and C_1-C_4 alkoxy; each R^9 and R^{10} are independently H or C_1-C_4 alkyl; R^{11} is selected from R^7 except H.

In a tenth preferred embodiment of the compound of formula 1:

the preferred groups as indicated for the ninth preferred embodiment, but:

Z^1 is H, Z^2 is OH; or Z^1 is methyl, Z^2 is OH; or Z^1 is H, Z^2 is NH_2; or both Z^1 and Z^2 are H; or Z^1 is H, Z^2 is F;

W^1 is H, W^2 is OH;

R^1 and R^2 are taken together as $=C(R^5)X^1\text{-}X^2\text{-}R^8$; wherein X^1 is $-CH_2-$, and X^2 is selected from $-S(O)_n-$ wherein n is 0 to 2, $-NR^9-$, and O; where X^2 is $-NR^9-$, then R^8 and R^9 may be taken together to form a 5 to 12 membered heterocyclic, which is optionally substituted by 1 to 3 R^6 groups;

and where R^5 is H or C_1-C_6 alkyl, wherein the foregoing R^5 alkyl group is optionally substituted by 1 or 2 R^6 groups:

and where R^8 is R^3, wherein R^3 is $-(CH_2)_t(C_6\text{-}C_{10}$ aryl) or $-(CH_2)_t$(4 to 10 membered heterocyclic), wherein each t is independently an integer from 0 to 2, and the foregoing R^3 groups are optionally substituted by 1 to 5 R^6 groups; wherein each R^6 is independently C_1-C_4 alkyl, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-OR^7$, $-C(O)R^7$, $-(CH_2)_m(C_6\text{-}C_{10}$ aryl), $-O(CH_2)_m(C_6\text{-}C_{10}$ aryl), and $-(CH_2)_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer from 0 to 2; said alkyl, aryl and heterocyclic R^6 groups are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-C(O)R^7$, $-NR^9C(O)OR^{11}$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, $-OR^7$, and C_1-C_4 alkyl;

each R^7 is independently selected from H and C_1-C_4 alkyl; the foregoing R^7 substituents, except H, are optionally substituted by 1 to 3 substituents independently selected from oxo, trifluoromethyl, $-C(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)NR^9R^{10}$, $-NR^9R^{10}$, hydroxy, and C_1-C_4 alkoxy; each R^9 and R^{10} are independently H, C_1-C_4 alkyl; R^{11} is selected from R^7 except H; R^{12} is C_1-C_4 alkyl except that R^{12} cannot be methyl if (a) X is OH, Y is O, W^1 is H, W^2 is α-OH, Z^1 is H, Z^2 is β-OH, or if (b) X is OH, Y is O, W^1 is H, W^2 is α-OH, Z^1 is H, Z^2 is H.

In an eleventh preferred embodiment of the compound of formula 1:

the preferred groups as indicated for the tenth preferred embodiment, but:

R^1 and R^2 are taken together as $=C(R^5)X^1\text{-}X^2\text{-}R^8$; wherein R^5 is H, X^1 is $-CH_2-$, and X^2 is O, and wherein R^8 is R^3, wherein R^3 is phenyl or (5 to 6 membered heterocyclic), and the foregoing R^8 groups are optionally substituted by 1 to 5 R^6 groups, wherein each R^6 is independently selected from C_1-C_4 alkyl, halo, trifluoromethyl, and $-(CH_2)_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 1; said heterocyclic R^6 groups are optionally substituted by 1 to 5 substituents independently selected from halo, trifluoromethyl, and C_1-C_4 alkyl.

In a twelfth preferred embodiment of the compound of formula 1:

the preferred groups as indicated for the first preferred embodiment, but:

R^1 is H and R^2 is $-NR^3R^4$, $-NR^4C(O)R^3$, $-OC(O)NR^3R^4$ or $-OR^3$ and the preferred configuration of the 1" center is that of hygromycin A.

In a thirteenth preferred embodiment of the compound of formula 1:

the preferred groups as indicated for the twelfth preferred embodiment, but:

X is F, H or OH;

Y is O;

W^1 is R^3, W^2 is OR^{13}; or W^1 is H, W^2 is R^3 or F; Z^1 is R^3, Z^2 is OR^{13}; or Z^1 is H, Z^2 is R^3 or F; wherein each R^3 and R^{13} are independently H or C_1-C_4 alkyl, and said alkyl groups are optionally substituted by 1 to 3 R^6 groups; wherein each R^6 is independently halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-OR^7$, $-C(O)R^7$, $-NR^9C(O)OR^{11}$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, or $-NR^7R^9$; wherein each R^7 and R^9 are independently H or C_1-C_4 alkyl; R^{11} is C_1-C_4 alkyl;

and in the substituent R^2, R^3 is independently selected from H, C_1-C_{10} alkyl, $-(CR^9R^{10})_t(C_3$-C_{10} cycloalkyl), $-(CR^9R^{10})_t(C_6$-C_{10} aryl), and $-(CR^9R^{10})_t$(4 to 10 membered heterocyclic), wherein each t is independently an integer from 0 to 3, said alkyl group optionally contains 1 hetero moiety selected from O, $-S(O)_j-$ wherein j is an integer ranging from 0 to 2, and $-N(R^9)-$; said cycloalkyl, aryl and heterocyclic R^3 groups are optionally fused to a benzene ring, a C_5-C_8 cycloalkyl group, or a 4 to 10 membered heterocyclic group; and the foregoing R^3 groups, except H but including any optional fused rings referred to above, are optionally substituted by 1 to 5 R^6 groups, and with the proviso that R^3 must be attached through a carbon atom unless R^3 is H; each R^4 is independently H or C_1-C_6 alkyl; each R^6 is independently C_1-C_4 alkyl, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-OR^7$, $-C(O)R^7$, $-NR^9C(O)OR^{11}$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, $-NR^7R^9$, $-(CR^9R^{10})_m(C_6$-C_{10} aryl), $-O(CR^9R^{10})_m(C_6$-C_{10} aryl), $-NR^9(CR^9R^{10})_m(C_6$-C_{10} aryl), and $-(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 2; said alkyl, aryl and heterocyclic R^6 groups are optionally substituted by 1 to 5 substituents independently selected from halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-NR^9SO_2R^{11}$, $-C(O)R^7$, $-NR^9C(O)OR^{11}$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, $-NR^7R^9$, $-OR^7$, and C_1-C_4 alkyl; each R^7 is independently selected from H, C_1-C_4 alkyl, C_3-C_8 cycloalkyl, $-(CR^9R^{10})_m(C_6$-C_{10} aryl), and $-(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 2; the foregoing R^7 substituents, except H, are optionally substituted by 1 to 5 substituents independently selected from halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-C(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)NR^9R^{10}$, $-NR^9R^{10}$, hydroxy, C_1-C_4 alkyl, and C_1-C_4 alkoxy; each R^9 and R^{10} are independently H, C_1-C_4 alkyl; R^{11} is selected from R^7 except H; R^{12} is C_1-C_4 alkyl except that R^{12} cannot be methyl if (a) X is OH, Y is O, W^1 is H, W^2 is α-OH, Z^1 is H, Z^2 is β-OH, or if (b) X is OH, Y is O, W^1 is H, W^2 is α-OH, Z^1 is H, Z^2 is H.

In a fourteenth preferred embodiment of the compound of formula 1:

V is $R^3OC(O)$, $R^3R^4NC(O)$ or $R^3O(R^4)NC(O)$ and the preferred configuration of the 1" center is that of hygromycin A.

In a fifteenth preferred embodiment of the compound of formula 1:

the preferred groups as indicated for the fourteenth preferred embodiment, but:

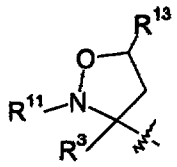
X is F, H or OH;

Y is O;

W^1 is R^3, W^2 is OR^{13}; or W^1 is H, W^2 is R^3 or F; Z^1 is R^3, Z^2 is OR^{13}; or Z^1 is H, Z^2 is R^3 or F; wherein each R^3 and R^{13} are independently H or C_1-C_4 alkyl, and said alkyl groups are optionally substituted by 1 to 3 R^6 groups; wherein each R^6 is independently halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-OR^7$, $-C(O)R^7$, $-NR^9C(O)OR^{11}$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, or $-NR^7R^9$; wherein each R^7 and R^9 are independently H or C_1-C_4 alkyl; R^{11} is C_1-C_4 alkyl;

within substituent V, R^3 is independently selected from H, C_1-C_{10} alkyl, $-(CR^9R^{10})_t(C_3$-C_{10} cycloalkyl), $-(CR^9R^{10})_t(C_6$-C_{10} aryl), and $-(CR^9R^{10})_t$(4 to 10 membered heterocyclic), wherein each t is independently an integer ranging from 0 to 3, said alkyl group optionally contains 1 hetero moiety selected from O, $-S(O)_j-$ wherein j is an integer ranging from 0 to 2, and $-N(R^9)-$; said cycloalkyl, aryl and heterocyclic R^3 groups are optionally fused to a benzene ring, a C_5-C_8 cycloalkyl group, or a 4 to 10 membered heterocyclic group; and the foregoing R^3 groups, except H but including any optional fused rings referred to above, are optionally substituted by 1 to 5 R^6 groups, and with the proviso that R^3 must be attached through a carbon atom unless R^3 is H; each R^4 is independently H or C_1-C_6 alkyl; each R^6 is independently C_1-C_4 alkyl, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-OR^7$, $-C(O)R^7$, $-NR^9C(O)OR^{11}$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, $-NR^7R^9$, $-(CR^9R^{10})_m(C_6$-C_{10} aryl), $-O(CR^9R^{10})_m(C_6$-C_{10} aryl), $-NR^9(CR^9R^{10})_m(C_6$-C_{10} aryl), and $-(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 2; said alkyl, aryl and heterocyclic R^6 groups are optionally substituted by 1 to 5 substituents independently selected from halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-NR^9SO_2R^{11}$, $-C(O)R^7$, $-NR^9C(O)OR^{11}$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, $-NR^7R^9$, $-OR^7$, C_1-C_4 alkyl; R^7 is independently selected from H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, $-(CR^9R^{10})_m(C_6$-C_{10} aryl), and $-(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 2; the foregoing R^7 substituents, except H, are optionally substituted by 1 to 5 substituents independently selected from halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-C(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)NR^9R^{10}$, $-NR^9R^{10}$, hydroxy, C_1-C_4 alkyl, and C_1-C_4 alkoxy; each R^9 and R^{10} are independently H and C_1-C_4 alkyl; R^{11} is selected from R^7 except H.

In a sixteenth preferred embodiment of the compound of formula 1:

V is a moiety of the structure  and the preferred configuration of the 1" center is that of hygromycin A.

In a seventeenth preferred embodiment of the compound of formula 1:

the preferred groups as indicated for the sixteenth preferred embodiment, but:

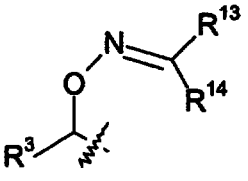
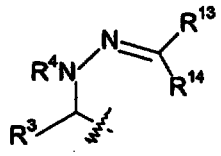
X is F, H or OH;

Y is O;

W^1 is R^3, W^2 is OR^{13}; or W^1 is H, W^2 is R^3 or F; Z^1 is R^3, Z^2 is OR^{13}; or Z^1 is H, Z^2 is R^3 or F; wherein each R^3 and R^{13} are independently H or C_1-C_4 alkyl, and said alkyl groups are optionally substituted by 1 to 3 R^6 groups; wherein each R^6 is independently halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-OR^7$, $-C(O)R^7$, $-NR^9C(O)OR^{11}$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, or $-NR^7R^9$; wherein each R^7 and R^9 is H or C_1-C_4 alkyl; R^{11} is C_1-C_4 alkyl;

within the substituent V, R^3 is C_1-C_6 alkyl; each R^{13} is independently selected from H, C_1-C_{10} alkyl, $-(CR^9R^{10})_t(C_3$-C_{10} cycloalkyl), $-(CR^9R^{10})_t(C_6$-C_{10} aryl), and $-(CR^9R^{10})_t$(4 to 10 membered heterocyclic), wherein each t is independently an integer ranging from 0 to 3, said alkyl group optionally contains 1 hetero moiety selected from O, $-S(O)_j-$ wherein j is an integer ranging from 0 to 2, and $-N(R^9)-$; said cycloalkyl, aryl and heterocyclic R^3 groups are optionally fused to a benzene ring, a C_5-C_8 cycloalkyl group, or a 4 to 10 membered heterocyclic group; and the foregoing R^3 groups, except H but including any optional fused rings referred to above, are optionally substituted by 1 to 5 R^6 groups, and with the proviso that R^3 must be attached through a carbon atom unless R^3 is H; each R^6 is independently C_1-C_4 alkyl, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-OR^7$, $-C(O)R^7$, $-NR^9C(O)OR^{11}$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, $-NR^7R^9$, $-(CR^9R^{10})_m(C_6$-C_{10} aryl), $-O(CR^9R^{10})_m(C_6$-C_{10} aryl), $-NR^9(CR^9R^{10})_m(C_6$-C_{10} aryl), and $-(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 2; said alkyl, aryl and heterocyclic R^6 groups are optionally substituted by 1 to 5 substituents independently selected from halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-NR^9SO_2R^{11}$, $-C(O)R^7$, $-NR^9C(O)OR^{11}$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, $-NR^7R^9$, $-OR^7$, and C_1-C_4 alkyl; each R^7 is independently selected from H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, $-(CR^9R^{10})_m(C_6$-C_{10} aryl), and $-(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 2; the foregoing R^7 substituents, except H, are optionally substituted by 1 to 5 substituents independently selected from halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-C(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)NR^9R^{10}$, $-NR^9R^{10}$, hydroxy, C_1-C_4 alkyl, and C_1-C_4 alkoxy; each R^9 and R^{10} are independently H or C_1-C_4 alkyl; R^{11} is selected from R^7 except H.

In a eighteenth preferred embodiment of the compound of formula 1:

V is a group of the structure  or , where both E and Z isomers are included and the preferred configuration of the 1" center is that of hygromycin A.

In a nineteenth preferred embodiment of the compound of formula 1:

the preferred groups as indicated for the eighteenth preferred embodiment, but:

X is F, H or OH;

Y is O;

R^{13} is $-(CR^9R^{10})_t(C_6\text{-}C_{10}$ aryl) or $-(CR^9R^{10})_t$(4 to 10 membered heterocyclic), wherein each t is independently an integer ranging from 0 to 2, and the foregoing R^3 groups are optionally substituted by 1 to 5 R^6 groups; wherein each R^6 is independently $C_1\text{-}C_4$ alkyl, oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-OR^7$, $-C(O)R^7$, $-(CR^9R^{10})_m(C_6\text{-}C_{10}$ aryl), $-O(CR^9R^{10})_m(C_6\text{-}C_{10}$ aryl), or $-(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 2; said alkyl, aryl and heterocyclic R^6 groups are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-C(O)R^7$, $-NR^9C(O)OR^{11}$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, $-OR^7$, and $C_1\text{-}C_4$ alkyl; each R^7 is independently selected from H and $C_1\text{-}C_4$ alkyl; the foregoing R^7 substituents, except H, are optionally substituted by 1 to 3 substituents independently selected from trifluoromethyl, $-C(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)NR^9R^{10}$, $-NR^9R^{10}$, hydroxy, and $C_1\text{-}C_4$ alkoxy; each R^9 and R^{10} are independently H or $C_1\text{-}C_4$ alkyl;

each R^4 and R^{14} are independently selected from H and $C_1\text{-}C_4$ alkyl;

R^3 is $C_1\text{-}C_4$ alkyl, and said alkyl group is optionally substituted by 1 to 3 R^6 groups; each R^6 is independently selected from $C_1\text{-}C_4$ alkyl, oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-OR^7$, $-C(O)R^7$, $-NR^9C(O)OR^{11}$, $-NR^9SO_2R^{11}$, $-SO_2NR^7R^9$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, $-NR^7R^9$, $-S(O)_j(CR^9R^{10})_m(C_6\text{-}C_{10}$ aryl), $-S(O)_j(C_1\text{-}C_6$ alkyl), wherein j is an integer ranging from 0 to 2, $-(CR^9R^{10})_m(C_6\text{-}C_{10}$ aryl), $-O(CR^9R^{10})_m(C_6\text{-}C_{10}$ aryl), $-NR^9(CR^9R^{10})_m(C_6\text{-}C_{10}$ aryl), and $-(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 2; and said alkyl, cycloalkyl, aryl and heterocyclic R^6 groups are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-NR^9SO_2R^{11}$, $-C(O)R^7$, $-NR^9C(O)OR^{11}$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, $-NR^7R^9$, $-OR^7$, $C_1\text{-}C_4$ alkyl, $-(CR^9R^{10})_m(C_6\text{-}C_{10}$ aryl), and $-(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 2; each R^7 is independently selected from H, $C_1\text{-}C_4$ alkyl, $C_3\text{-}C_6$ cycloalkyl,

$-(CR^9R^{10})_m(C_6\text{-}C_{10}$ aryl), and $-(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 2; said alkyl group optionally includes 1 hetero moiety selected from O, $-S(O)_j-$ wherein j is an integer ranging from 0 to 2, and $-N(R^9)-$; said cycloalkyl, aryl and heterocyclic R^7 groups are optionally fused to a $C_6\text{-}C_{10}$ aryl group, a $C_5\text{-}C_8$ cycloalkyl group, or a 4 to 10 membered heterocyclic group; and the foregoing R^7 substituents, except H, are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-C(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)NR^9R^{10}$, $-NR^9R^{10}$, hydroxy, $C_1\text{-}C_4$ alkyl, and $C_1\text{-}C_4$ alkoxy, and with the proviso that R^7 must be attached through a carbon atom unless R^7 is H; each R^9 and R^{10} are independently H or $C_1\text{-}C_4$ alkyl.

In a twentieth preferred embodiment of the compound of formula 1:

V is a carbon-linked 4 to 10 membered heterocyclic group, which may be optionally substituted by 1 to 3 R^6 groups and the preferred configuration of the 1" center is that of hygromycin A.

Specific preferred compounds of formula 1 include those listed below as well as the pharmaceutically acceptable salts, solvates and prodrugs of the following compounds:

1. 3-(3-Fluoro-4-((2S,4S,5R)-4-hydroxy-5-(1-methoxyimino-2-phenoxy-ethyl)-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide
2. 3-(4-((2S,4S,5R)-5-(1-((E)-4-Fluoro-benzyloxyimino)-2-hydroxy-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide
3. 3-(4-((2S,3S,4S,5R)-5-(5R-(3-Chloro-phenyl)-2,3-dimethyl-isoxazolidin-3-yl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide
4. (2S,3S,5S)-5-(2-Fluoro-4-(2-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-ylcarbamoyl)-propenyl)-phenoxy)-3-hydroxy-tetrahydro-furan-2-carboxylic acid benzyloxy-amide
5. 3-(4-((2S,4S,5R)-5-(((E)-2-Fluoro-4-chloro-benzyloxyimino)-methyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide
6. (2S,3S,4S,5S)-3,4-Dihydroxy-5-(2-hydroxy-4-(2-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-ylcarbamoyl)-propenyl)-phenoxy)-tetrahydro-furan-2-carboxylic acid benzyloxy-amide

7. (2S,3S,5S)-5-(2-Fluoro-4-(2-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-ylcarbamoyl)-propenyl)-phenoxy)-3-hydroxy-tetrahydro-furan-2-carboxylic acid benzylamide

8. 3-(4-((2R,4S,5S)-5-(1-((E)-2-Fluoro-4-chloro-benzyloxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

9. 3-(4-((2S,3S,5S)-5-(1-((E)-2,4-Dichloro-benzyloxyimino)-ethyl)-3-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

10. 3-(4-((2R,4S,5R)-5-(1-((E)-4-Fluoro-benzyloxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

11. 3-(4-((2S,3S,5S)-5-(1-((E)-3,4-Difluoro-benzyloxyimino)-ethyl)-3-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

12. 3-(4-((2S,5S)-5-(1-((E)-2-Chloro-5-fluoro-benzyloxyimino)-ethyl)-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

13. 3-(4-((2R,4S,5R)-5-(1-((E)-2,4-Dichloro-5-fluoro-benzyloxyimino)-ethyl)-4-methoxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

14. 3-(4-((2S,3S,4S,5R)-3-Amino-5-(1-((E)-3-chloro-benzyloxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

15. 3-(4-((2S,4S,5S)-5-(1-(3-Chloro-benzyloxy)-propyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-3-(4-((2S,4R,5R)-5-(1-((E)-2-Chloro-benzyloxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

16. 3-(4-((2S,4S,5R)-5-(1-((E)-Benzo(1,3)dioxol-5-ylmethoxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

17. 3-(4-((1R,3R,4R)-3-(1-((E)-Benzo(1,3)dioxol-5-ylmethoxyimino)-ethyl)-4-hydroxy-cyclopentyloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

18. 3-(4-((1R,3R,4R)-3-(((E)-Benzo(1,3)dioxol-5-ylmethoxyimino)-methyl)-4-hydroxy-cyclopentyloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

19. 3-(4-((2S,4S,5R)-5-(1-((E)-Benzo[1,3]dioxol-5-ylmethoxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

20. 3-(4-((2S,4S,5R)-5-(((E)-Benzo(1,3)dioxol-5-ylmethoxyimino)-methyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

21. 3-(4-((1R,2S,3R,4R)-4-(((E)-2,4-Dichloro-benzyloxyimino)-methyl)-2,3-dihydroxy-cyclopentyloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

22. 3-(4-((1S,3R,4R)-3-(1-((E)-2,3-Dichloro-5-fluoro-benzyloxyimino)-ethyl)-4-hydroxy-cyclopentyloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

23. 3-(4-((1R,2S,4R)-4-(1-((E)-3-Chloro-benzyloxyimino)-ethyl)-2-hydroxy-cyclopentyloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

24. 3-(4-((1S,3R)-3-(1-((E)-3,4-Difluoro-benzyloxyimino)-ethyl)-cyclopentyloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

25. 3-(4-((1R,2S,3R,4R)-4-(1-((E)-2-Fluoro-benzyloxyimino)-ethyl)-2,3-dihydroxy-cyclopentyloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

26. 3-(4-((2S,3S,4S,5S)-5-(1-(3-Chloro-benzylideneaminooxy)-ethyl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

27. 3-(4-((2S,4S,5S)-5-(1-(1-(4-Fluoro-phenyl)-ethylideneaminooxy)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

28. 3-(4-((2S,4S,5S)-5-(1-(1-(2,4-Dichloro-phenyl)-ethylideneaminooxy)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

29. 3-(4-((2S,3S,4S,5R)-5-(2-(2,4-Dichloro-benzyl)-thiazol-4-yl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

30. 3-(4-((2S,3S,4S,5R)-5-(3-(2,4-Dichloro-phenoxy)-1-hydroxymethyl-(E)-propenyl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

31. 3-(4-((2S,4S,5R)-5-(3-(2,4-Dichloro-phenoxy)-1-hydroxymethyl-(E)-propenyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

32. 3-(4-((1R,2S,3R,4S)-4-(3-(2,4-Dichloro-phenoxy)-(E)-propenyl)-2,3-dihydroxy-cyclopentyloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

33. 3-(4-(2S,3S,4S,5R)-5-(2-(2,4-Dichloro-benzyl)-3H-imidazol-4-yl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

34. 3-(4-((2S,3S,4S,5R)-5-(6-Chloro-1H-benzoimidazol-2-yl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

35. 3-(4-((2S,3S,4S,5R)-5-(1-(N'-(2,4-Dichloro-benzylidene)-hydrazino)-ethyl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

36. 3-(4-((2S,3S,4S,5R)-5-(1-(N'-(2-Chloro-benzylidene)-hydrazino)-ethyl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

37. 3-(4-((2S,4S,5R)5-(1-(N'-(2-Chloro-5-fluoro-benzylidene)-hydrazino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

38. 3-(4-((2S,4S,5R)-5-(1-(N'-(3-Chloro-benzylidene)-hydrazino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

39. 3-(4-((2S,4S,5R)-5-(1-((E)-3-Chloro-benzyloxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

40. 3-(4-((2S,3R,4S,5R)-5-(1-((E)-2,3-Dichloro-5-fluoro-benzyloxyimino)-ethyl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-

((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

41. 3-(4-((2S,3R,4S,5R)-5-(1-((E)-3-Chloro-benzyloxyimino)-ethyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

42. 3-(4-((2S,4S,5R)-5-(1-((E)-4-Fluoro-benzyloxyimino)-propyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

43. 3-(4-((2S,4S,5R)-5-((E)-1-Benzyloxyimino-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

44. 3-(4-((2S,3S,4R,5R)-5-(1-((E)-3-Chloro-benzyloxyimino)-ethyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

45. 3-(4-((2S,3S,4R,5R)-5-(1-((E)-3,4-Difluoro-benzyloxyimino)-ethyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

46. 3-(4-((2S,3R,4R,5R)-5-(1-((E)-3-Chloro-benzyloxyimino)-ethyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

47. 3-(3-Fluoro-4-((2S,4S,5R)-5-(1-((E)-3-fluoro-4-morpholin-4-yl-benzyloxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

48. 3-(3-Amino-4-((2S,4S,5R)-5-(1-((E)-4-fluoro-benzyloxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

49. 3-(4-((2S,4S,5R)-5-(3-(2,4-Dichloro-phenoxy)-1-methyl-(E)-propenyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

50. 3-(3-Amino-4-((2S,4S,5R)-5-(3-(2-chloro-5-fluoro-phenoxy)-1-methyl-(E)-propenyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

51. 3-(3-Amino-4-((2S,3R,4S,5R)-5-(1-((E)-2-chloro-benzyloxyimino)-ethyl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

52. 3-(4-((2S,3R,4S,5R)-5-(3-(2-Fluoro-phenoxy)-1-methyl-(E)-propenyl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

53. 3-(3-Amino-4-((2S,3R,4R,5R)-5-(3-(3-chloro-phenoxy)-1-methyl-(E)-propenyl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

54. 3-(4-((2S,3R,4R,5R)-5-(1-((E)- 3-Chloro-benzyloxyimino)-ethyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

55. 3-(3-Amino-4-((2S,3R,4R,5R)-5-(1-((E)-3-Chloro-benzyloxyimino)-ethyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

56. 3-(4-((2S,3R,4R,5R)-5-(3-(3,4-Difluoro-phenoxy)-1-methyl-(E)-propenyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

57. 3-(3-Amino-4-((2S,3R,4R,5R)-5-(3-(2-fluoro-4-chloro-phenoxy)-1-methyl-(E)-propenyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

58. 3-(4-((2S,4S,5R)-5-(1-((E)-4-Fluoro-benzyloxyimino)-propyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

59. 3-(3-Amino-4-((2S,4S,5R)-5-(1-((E)-2,4-dichloro-benzyloxyimino)-propyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

60. 3-(4-((2S,4S,5R)-5-(3-(3-Chloro-phenoxy)-1-ethyl-(E)-propenyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

61. 3-(3-Amino-4-((2S,4S,5R)-5-(3-(2,3-dichloro-5-fluoro-phenoxy)-1-ethyl-(E)-propenyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

62. 3-(3-Amino-4-((2S,4S,5R)-5-((E)-1-benzyloxyimino-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

63. 3-(3-Fluoro-4-((2S,4S,5R)-4-hydroxy-5-(1-methyl-3-phenoxy-(E)-propenyl)-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

64. 3-(3-Amino-4-((2S,4S,5R)-4-hydroxy-5-(1-methyl-3-phenoxy-(E)-propenyl)-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

65. 3-(4-((2S,3S,4R,5R)-5-(1-((E)-2-Chloro-5-fluoro-benzyloxyimino)-ethyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

66. 3-(3-Amino-4-((2S,3S,4R,5R)-5-(1-((E)-2-chloro-benzyloxyimino)-ethyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

67. 3-(4-((2S,3S,4R,5R)-5-(3-(3-Chloro-phenoxy)-1-methyl-(E)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

68. 3-(3-Amino-4-((2S,3S,4R,5R)-5-(3-(2-fluoro-phenoxy)-1-methyl-(E)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

69. 3-(4-((2S,3S,4R,5R)-5-(1-((E)-4-Fluoro-benzyloxyimino)-propyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

70. 3-(4-((2S,3S,4R,5R)-5-(1-((E)-3-Chloro-benzyloxyimino)-propyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

71. 3-(4-((2S,3S,4R,5R)-5-(3-(3-Chloro-phenoxy)-1-ethyl-(E)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

72. 3-(4-((2S,3S,4R,5R)-5-(3-(3-Chloro-phenoxy)-1-ethyl-(E)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-

((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

73. 3-(4-((2S,3R,4R,5R)-5-(1-((E)-3,4-Difluoro-benzyloxyimino)-ethyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

74. 3-(3-Amino-4-((2S,3R,4R,5R)-5-(1-((E)-2,3-dichloro-5-fluoro-benzyloxyimino)-ethyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

75. 3-(4-((2S,3R,4R,5R)-5-(3-(2-Chloro-5-fluoro-phenoxy)-1-methyl-(E)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

76. 3-(3-Amino-4-((2S,3R,4R,5R)-5-(3-(2-fluoro-4-chloro-phenoxy)-1-methyl-(E)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

77. 3-(3-Amino-4-((2S,4S,5R)-5-(1-((E)-3-fluoro-4-morpholin-4-yl-benzyloxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

78. 3-(3-Fluoro-4-((2S,4S,5R)-5-(3-(3-fluoro-4-morpholin-4-yl-phenoxy)-1-methyl-(E)-propenyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

79. 3-(3-Amino-4-((2S,4S,5R)-5-(3-(3-fluoro-4-morpholin-4-yl-phenoxy)-1-methyl-(E)-propenyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

80. 3-(4-((2S,3S,4R,5R)-5-(1-((E)-4-Fluoro-benzyloxyimino)-ethyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

81. 3-(4-((2S,3S,4R,5R)-5-(1-((E)-2-Fluoro-benzyloxyimino)-ethyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

82. 3-(3-Amino-4-((2S,3S,4R,5R)-5-(1-((E)-3-Chloro-benzyloxyimino)-ethyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

83. 3-(4-((2S,3S,4R,5R)-5-(3-(3-Chloro-phenoxy)-1-methyl-(E)-propenyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

84. 3-(3-Amino-4-((2S,3S,4R,5R)-5-(3-(3-chloro-phenoxy)-1-methyl-(E)-propenyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

85. 3-(4-((2S,3S,5S)-5-(1-((E)-2,4-Dichloro-benzyloxyimino)-ethyl)-3-fluoro-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

86. 3-(4-((2S,3S,5S)-5-(3-(3,4-Difluoro-phenoxy)-1-methyl-(E)-propenyl)-3-fluoro-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

87. 3-(4-((2S,3S,5S)-5-(1-((E)-2-Chloro-benzyloxyimino)-ethyl)-3-fluoro-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

88. 3-(4-((2S,3S,5S)-5-(3-(2-Fluoro-phenoxy)-1-methyl-(E)-propenyl)-3-fluoro-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

89. 3-(4-((2S,3R,5S)-5-(1-((E)-2-Fluoro-4-chloro-benzyloxyimino)-ethyl)-3-fluoro-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

90. 3-(4-((2S,3R,5S)-5-(3-(3-Chloro-phenoxy)-1-methyl-(E)-propenyl)-3-fluoro-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

91. 3-(4-((2S,3R,5S)-5-(1-((E)-2-Chloro-5-fluoro-benzyloxyimino)-ethyl)-3-fluoro-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

92. 3-(4-((2S,3R,5S)-5-(3-(3-Chloro-phenoxy)-1-methyl-(E)-propenyl)-3-fluoro-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

93. 3-(4-((2S,3R,4R,5R)-5-(3-(3-Chloro-phenoxy)-1-methyl-(E)-propenyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

94. 3-(4-((2S,4S,5R)-5-(3-(3,4-Difluoro-phenoxy)-1-ethyl-(E)-propenyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

95. 3-(4-((2S,3S,4R,5R)-5-(3-(2-Chloro-5-fluoro-phenoxy)-1-methyl-(E)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

96. 3-(4-((2S,3S,4R,5R)-5-(3-(2-Fluoro-4-chloro-phenoxy)-1-methyl-(E)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

97. 3-(4-((2S,3R,4R,5R)-5-(3-(2,4-Dichloro-phenoxy)-1-methyl-(E)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

98. 3-(4-((2S,4S,5R)-5-(3-(3-Chloro-phenoxy)-1-methyl-(Z)-propenyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

99. 3-(3-Amino-4-((2S,4S,5R)-5-(3-(2-chloro-phenoxy)-1-methyl-(Z)-propenyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

100. 3-(4-((2S,3R,4S,5R)-5-(3-(2-Fluoro-phenoxy)-1-methyl-(Z)-propenyl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

101. 3-(3-Amino-4-((2S,3R,4S,5R)-5-(3-(3-chloro-phenoxy)-1-methyl-(Z)-propenyl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

102. 3-(4-((2S,3R,4R,5R)-5-(3-(3,4-Difluoro-phenoxy)-1-methyl-(Z)-propenyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

103. 3-(4-((2S,3R,4R,5R)-5-(3-(4-Fluoro-phenoxy)-1-methyl-(Z)-propenyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

104. 3-(3-Amino-4-((2S,3R,4R,5R)-5-(3-(2-fluoro-4-chloro-phenoxy)-1-methyl-(Z)-propenyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

105. 3-(4-((2S,4S,5R)-5-(3-(3-Chloro-phenoxy)-1-ethyl-(Z)-propenyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

106. 3-(4-((2S,4S,5R)-5-(3-(2,3-Dichloro-5-fluoro-phenoxy)-1-ethyl-(Z)-propenyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

107. 3-(3-Amino-4-((2S,4S,5R)-5-(3-(2-fluoro-phenoxy)-1-ethyl-(Z)-propenyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

108. 3-(3-Fluoro-4-((2S,4S,5R)-4-hydroxy-5-(1-methyl-3-phenoxy-(Z)-propenyl)-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

109. 3-(3-Amino-4-((2S,4S,5R)-4-hydroxy-5-(1-methyl-3-phenoxy-(Z)-propenyl)-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

110. 3-(4-((2S,3S,4R,5R)-5-(3-(2-Chloro-5-fluoro-phenoxy)-1-methyl-(Z)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

111. 3-(4-((2S,3S,4R,5R)-5-(3-(3-Chloro-phenoxy)-1-methyl-(Z)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

112. 3-(3-Amino-4-((2S,3S,4R,5R)-5-(3-(2,4-dichloro-phenoxy)-1-methyl-(Z)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

113. 3-(4-((2S,3S,4R,5R)-5-(3-(3,4-Difluoro-phenoxy)-1-ethyl-(Z)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

114. 3-(4-((2S,3S,4R,5R)-5-(3-(2-Chloro-phenoxy)-1-ethyl-(Z)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

115. 3-(4-((2S,3S,4R,5R)-5-(3-(2-Fluoro-4-chloro-phenoxy)-1-ethyl-(Z)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

116. 3-(4-((2S,3R,4R,5R)-5-(3-(3-Chloro-phenoxy)-1-methyl-(Z)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

117. 3-(4-((2S,3R,4R,5R)-5-(3-(3-Chloro-phenoxy)-1-methyl-(Z)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

118. 3-(3-Amino-4-((2S,3R,4R,5R)-5-(3-(2,4-dichloro-phenoxy)-1-methyl-(Z)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

119. 3-(3-Fluoro-4-((2S,4S,5R)-5-(3-((E)-3-fluoro-4-morpholin-4-yl-phenoxy)-1-methyl-(Z)-propenyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

120. 3-(3-Amino-4-((2S,4S,5R)-5-(3-((E)-3-fluoro-4-morpholin-4-yl-phenoxy)-1-methyl-(Z)-propenyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

121. 3-(4-((2S,3R,4S,5R)-3-Amino-5-(1-((E)-3,4-difluoro-benzyloxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

122. 3-(4-((2S,3S,4R,5R)-5-(3-(3-Chloro-phenoxy)-1-methyl-(Z)-propenyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

123. 3-(3-Amino-4-((2S,3S,4R,5R)-5-(3-(4-fluoro-phenoxy)-1-methyl-(Z)-propenyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

124. 3-(4-((2S,3S,4S,5R)-5-(1-((E)-2-Fluoro-benzyloxyimino)-ethyl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

125. 3-(3-Amino-4-((2S,3S,4S,5R)-5-(1-((E)-2-chloro-5-fluoro-benzyloxyimino)-ethyl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

126. 3-(4-((2S,3S,4S,5R)-5-(3-(3-Chloro-phenoxy)-1-methyl-(E)-propenyl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

127. 3-(3-Amino-4-((2S,3S,4S,5R)-5-(3-(2,4-dichloro-phenoxy)-1-methyl-(E)-propenyl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

128. 3-(4-((2S,3S,4S,5R)-5-(3-(2-Fluoro-4-chloro-phenoxy)-1-methyl-(Z)-propenyl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

129. 3-(3-Amino-4-((2S,3S,4S,5R)-5-(3-(3,4-difluoro-phenoxy)-1-methyl-(Z)-propenyl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

130. 3-(4-((2S,3S,4S,5R)-5-(5S-(3-Chloro-phenyl)-2,3-dimethyl-isoxazolidin-3-yl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

131. 3-(4-((2S,4S,5R)-5-(1-((Z)-2-Chloro-benzyloxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

132. 3-(4-((2S,3R,4S,5R)-5-(1-((Z)-2,4-Dichloro-5-fluoro-benzyloxyimino)-ethyl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-

((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

133. 3-(4-((2S,3R,4S,5R)-5-(1-((Z)-2-Chloro-benzyloxyimino)-ethyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

134. 3-(4-((2S,4S,5R)-5-(1-((Z)-3,4-Difluoro-benzyloxyimino)-propyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

135. 3-(4-((2S,4S,5R)-5-((Z)-1-Benzyloxyimino-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

136. 3-(4-((2S,3S,4R,5R)-5-(1-((Z)-2-Fluoro-benzyloxyimino)-ethyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

137. 3-(4-((2S,3S,4R,5R)-5-(1-((Z)-2,4-Dichloro-benzyloxyimino)-ethyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

138. 3-(4-((2S,3R,4R,5R)-5-(1-((Z)-2,4-Dichloro-benzyloxyimino)-ethyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

139. 3-(3-Fluoro-4-((2S,4S,5R)-5-(1-((Z)-3-fluoro-4-morpholin-4-yl-benzyloxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

140. 3-(3-Amino-4-((2S,4S,5R)-5-(1-((Z)-2-fluoro-4-chloro-benzyloxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

141. 3-(4-((2S,3R,4R,5R)-5-(1-((Z)-2-Chloro-benzyloxyimino)-ethyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

142. 3-(3-Amino-4-((2S,3R,4R,5R)-5-(1-((Z)-2-chloro-5-fluoro-benzyloxyimino)-ethyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

143. 3-(4-((2S,4S,5R)-5-(1-((Z)-3-Chloro-benzyloxyimino)-propyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

144. 3-(3-Amino-4-((2S,4S,5R)-5-(1-((Z)-3-Chloro-benzyloxyimino)-propyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

145. 3-(4-((2S,3S,4R,5R)-5-(1-((Z)-2-Chloro-benzyloxyimino)-propyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

146. 3-(4-((2S,3S,4R,5R)-5-(1-((Z)-3-Chloro-benzyloxyimino)-propyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

147. 3-(3-Amino-4-((2S,4S,5R)-5-(1-((Z)-3-fluoro-4-morpholin-4-yl-benzyloxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

148. 3-(4-((2S,3S,4R,5R)-5-(1-((Z)-2,4-Dichloro-benzyloxyimino)-ethyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

149. 3-(3-Amino-4-((2S,3S,4R,5R)-5-(1-((Z)-2-fluoro-benzyloxyimino)-ethyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

150. 3-(4-((2S,4S,5R)-5-(1-((E)-3,4-Difluoro-benzyloxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide.

151. 3-(4-((2S,4R,5R)-5-(1-((E)-3-Chloro-benzyloxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

152. 3-(4-((2S,4R,5R)-5-(3-(2,4-Dichloro-phenoxy)-1-methyl-(E)-propenyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

153. 3-(3-Fluoro-4-((2S,4R,5R)-4-hydroxy-5-(1-((E)-4-piperidin-1-yl-benzyloxyimino)-ethyl)-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

154. 3-(4-((2S,4R,5R)-5-(1-((E)-3-Chloro-benzyloxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

155. 3-(3-Fluoro-4-((2S,4R,5R)-4-hydroxy-5-(1-((E)-4-morpholin-4-yl-benzyloxyimino)-ethyl)-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

156. 3-(4-((2S,3S,4R,5R)-5-(1-((E)-3-Chloro-benzyloxyimino)-ethyl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-(4,6,7-trihydroxy-hexahydro-benzo[1,3]dioxol-5-yl)-(2E)-acrylamide

157. 3-(3-Fluoro-4-((2S,4R,5R)-5-(1-((E)-3-fluoro-4-piperidin-1-yl-benzyloxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

Additional preferred compounds of formula 1, which are more preferred than those referred to above, include those listed below as well as the pharmaceutically acceptable salts, solvates and prodrugs of the following compounds:

1. 3-(4-((2S,4S,5R)-5-(1-((E)-3-Chloro-benzyloxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

2. 3-(4-((2S,3R,4S,5R)-5-(1-((E)-2,3-Dichloro-5-fluoro-benzyloxyimino)-ethyl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

3. 3-(4-((2S,3R,4S,5R)-5-(1-((E)-3-Chloro-benzyloxyimino)-ethyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

4. 3-(4-((2S,4S,5R)-5-(1-((E)-4-Fluoro-benzyloxyimino)-propyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

5. 3-(4-((2S,4S,5R)-5-((E)-1-Benzyloxyimino-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

6. 3-(4-((2S,3S,4R,5R)-5-(1-((E)-3-Chloro-benzyloxyimino)-ethyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

7. 3-(4-((2S,3S,4R,5R)-5-(1-((E)-3,4-Difluoro-benzyloxyimino)-ethyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

8. 3-(4-((2S,3R,4R,5R)-5-(1-((E)-3-Chloro-benzyloxyimino)-ethyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

9. 3-(3-Fluoro-4-((2S,4S,5R)-5-(1-((E)-3-fluoro-4-morpholin-4-yl-benzyloxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

10. 3-(3-Amino-4-((2S,4S,5R)-5-(1-((E)-4-fluoro-benzyloxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

11. 3-(4-((2S,4S,5R)-5-(3-(2,4-Dichloro-phenoxy)-1-methyl-(E)-propenyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

12. 3-(3-Amino-4-((2S,4S,5R)-5-(3-(2-chloro-5-fluoro-phenoxy)-1-methyl-(E)-propenyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

13. 3-(3-Amino-4-((2S,3R,4S,5R)-5-(1-((E)-2-chloro-benzyloxyimino)-ethyl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

14. 3-(4-((2S,3R,4S,5R)-5-(3-(2-Fluoro-phenoxy)-1-methyl-(E)-propenyl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

15. 3-(3-Amino-4-((2S,3R,4R,5R)-5-(3-(3-chloro-phenoxy)-1-methyl-(E)-propenyl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

16. 3-(4-((2S,3R,4R,5R)-5-(1-((E)-2-Fluoro-benzyloxyimino)-ethyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

17. 3-(3-Amino-4-((2S,3R,4R,5R)-5-(1-((E)-3-Chloro-benzyloxyimino)-ethyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

18. 3-(4-((2S,3R,4R,5R)-5-(3-(3,4-Difluoro-phenoxy)-1-methyl-(E)-propenyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

19. 3-(3-Amino-4-((2S,3R,4R,5R)-5-(3-(2-fluoro-4-chloro-phenoxy)-1-methyl-(E)-propenyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

20. 3-(4-((2S,4S,5R)-5-(1-((E)-4-Fluoro-benzyloxyimino)-propyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

21. 3-(3-Amino-4-((2S,4S,5R)-5-(1-((E)-2,4-dichloro-benzyloxyimino)-propyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

22. 3-(4-((2S,4S,5R)-5-(3-(3-Chloro-phenoxy)-1-ethyl-(E)-propenyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

23. 3-(3-Amino-4-((2S,4S,5R)-5-(3-(2,3-dichloro-5-fluoro-phenoxy)-1-ethyl-(E)-propenyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

24. 3-(3-Amino-4-((2S,4S,5R)-5-((E)-1-benzyloxyimino-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

25. 3-(3-Fluoro-4-((2S,4S,5R)-4-hydroxy-5-(1-methyl-3-phenoxy-(E)-propenyl)-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

26. 3-(3-Amino-4-((2S,4S,5R)-4-hydroxy-5-(1-methyl-3-phenoxy-(E)-propenyl)-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

27. 3-(4-((2S,3S,4R,5R)-5-(1-((E)-2-Chloro-5-fluoro-benzyloxyimino)-ethyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

28. 3-(3-Amino-4-((2S,3S,4R,5R)-5-(1-((E)-2-chloro-benzyloxyimino)-ethyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

29. 3-(4-((2S,3S,4R,5R)-5-(3-(3-Chloro-phenoxy)-1-methyl-(E)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

30. 3-(3-Amino-4-((2S,3S,4R,5R)-5-(3-(2-fluoro-phenoxy)-1-methyl-(E)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

31. 3-(4-((2S,3S,4R,5R)-5-(1-((E)-4-Fluoro-benzyloxyimino)-propyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

32. 3-(4-((2S,3S,4R,5R)-5-(1-((E)-3-Chloro-benzyloxyimino)-propyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

33. 3-(4-((2S,3S,4R,5R)-5-(3-(3-Chloro-phenoxy)-1-ethyl-(E)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

34. 3-(4-((2S,3S,4R,5R)-5-(3-(3-Chloro-phenoxy)-1-ethyl-(E)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

35. 3-(4-((2S,3R,4R,5R)-5-(1-((E)-3,4-Difluoro-benzyloxyimino)-ethyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

36. 3-(3-Amino-4-((2S,3R,4R,5R)-5-(1-((E)-2,3-dichloro-5-fluoro-benzyloxyimino)-ethyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

37. 3-(4-((2S,3R,4R,5R)-5-(3-(2-Chloro-5-fluoro-phenoxy)-1-methyl-(E)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

38. 3-(3-Amino-4-((2S,3R,4R,5R)-5-(3-(2-fluoro-4-chloro-phenoxy)-1-methyl-(E)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-

((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

39. 3-(3-Amino-4-((2S,4S,5R)-5-(1-((E)-3-fluoro-4-morpholin-4-yl-benzyloxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

40. 3-(3-Fluoro-4-((2S,4S,5R)-5-(3-(3-fluoro-4-morpholin-4-yl-phenoxy)-1-methyl-(E)-propenyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

41. 3-(3-Amino-4-((2S,4S,5R)-5-(3-(3-fluoro-4-morpholin-4-yl-phenoxy)-1-methyl-(E)-propenyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

42. 3-(4-((2S,3S,4R,5R)-5-(1-((E)-4-Fluoro-benzyloxyimino)-ethyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

43. 3-(4-((2S,3S,4R,5R)-5-(1-((E)-3-Chloro-benzyloxyimino)-ethyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

44. 3-(3-Amino-4-((2S,3S,4R,5R)-5-(1-((E)-3-Chloro-benzyloxyimino)-ethyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

45. 3-(4-((2S,3S,4R,5R)-5-(3-(3-Chloro-phenoxy)-1-methyl-(E)-propenyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

46. 3-(3-Amino-4-((2S,3S,4R,5R)-5-(3-(3-chloro-phenoxy)-1-methyl-(E)-propenyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

47. 3-(4-((2S,3S,5S)-5-(1-((E)-2,4-Dichloro-benzyloxyimino)-ethyl)-3-fluoro-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

48. 3-(4-((2S,3S,5S)-5-(3-(3,4-Difluoro-phenoxy)-1-methyl-(E)-propenyl)-3-fluoro-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

49. 3-(4-((2S,3S,5S)-5-(1-((E)-2-Chloro-benzyloxyimino)-ethyl)-3-fluoro-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

50. 3-(4-((2S,3S,5S)-5-(3-(2-Fluoro-phenoxy)-1-methyl-(E)-propenyl)-3-fluoro-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

51. 3-(4-((2S,3R,5S)-5-(1-((E)-2-Fluoro-4-chloro-benzyloxyimino)-ethyl)-3-fluoro-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

52. 3-(4-((2S,3R,5S)-5-(3-(3-Chloro-phenoxy)-1-methyl-(E)-propenyl)-3-fluoro-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

53. 3-(4-((2S,3R,5S)-5-(1-((E)-2-Chloro-5-fluoro-benzyloxyimino)-ethyl)-3-fluoro-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

54. 3-(4-((2S,3R,5S)-5-(3-(3-Chloro-phenoxy)-1-methyl-(E)-propenyl)-3-fluoro-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

55. 3-(4-((2S,3R,4R,5R)-5-(3-(3-Chloro-phenoxy)-1-methyl-(E)-propenyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

56. 3-(4-((2S,4S,5R)-5-(3-(3,4-Difluoro-phenoxy)-1-ethyl-(E)-propenyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

57. 3-(4-((2S,3S,4R,5R)-5-(3-(2-Chloro-5-fluoro-phenoxy)-1-methyl-(E)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

58. 3-(4-((2S,3S,4R,5R)-5-(3-(2-Fluoro-4-chloro-phenoxy)-1-methyl-(E)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

59. 3-(4-((2S,3R,4R,5R)-5-(3-(2,4-Dichloro-phenoxy)-1-methyl-(E)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

60. 3-(4-((2S,4S,5R)-5-(3-(3-Chloro-phenoxy)-1-methyl-(Z)-propenyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

61. 3-(3-Amino-4-((2S,4S,5R)-5-(3-(2-chloro-phenoxy)-1-methyl-(Z)-propenyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

62. 3-(4-((2S,3R,4S,5R)-5-(3-(2-Fluoro-phenoxy)-1-methyl-(Z)-propenyl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

63. 3-(3-Amino-4-((2S,3R,4S,5R)-5-(3-(3-chloro-phenoxy)-1-methyl-(Z)-propenyl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

64. 3-(4-((2S,3R,4R,5R)-5-(3-(3,4-Difluoro-phenoxy)-1-methyl-(Z)-propenyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

65. 3-(4-((2S,3R,4R,5R)-5-(3-(4-Fluoro-phenoxy)-1-methyl-(Z)-propenyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

66. 3-(3-Amino-4-((2S,3R,4R,5R)-5-(3-(2-fluoro-4-chloro-phenoxy)-1-methyl-(Z)-propenyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

67. 3-(4-((2S,4S,5R)-5-(3-(3-Chloro-phenoxy)-1-ethyl-(Z)-propenyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

68. 3-(4-((2S,4S,5R)-5-(3-(2,3-Dichloro-5-fluoro-phenoxy)-1-ethyl-(Z)-propenyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

69. 3-(3-Amino-4-((2S,4S,5R)-5-(3-(2-fluoro-phenoxy)-1-ethyl-(Z)-propenyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

70. 3-(3-Fluoro-4-((2S,4S,5R)-4-hydroxy-5-(1-methyl-3-phenoxy-(Z)-propenyl)-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

71. 3-(3-Amino-4-((2S,4S,5R)-4-hydroxy-5-(1-methyl-3-phenoxy-(Z)-propenyl)-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

72. 3-(4-((2S,3S,4R,5R)-5-(3-(2-Chloro-5-fluoro-phenoxy)-1-methyl-(Z)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

73. 3-(4-((2S,3S,4R,5R)-5-(3-(3-Chloro-phenoxy)-1-methyl-(Z)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

74. 3-(3-Amino-4-((2S,3S,4R,5R)-5-(3-(2,4-dichloro-phenoxy)-1-methyl-(Z)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

75. 3-(4-((2S,3S,4R,5R)-5-(3-(3,4-Difluoro-phenoxy)-1-ethyl-(Z)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

76. 3-(4-((2S,3S,4R,5R)-5-(3-(2-Chloro-phenoxy)-1-ethyl-(Z)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

77. 3-(4-((2S,3S,4R,5R)-5-(3-(2-Fluoro-4-chloro-phenoxy)-1-ethyl-(Z)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

78. 3-(4-((2S,3R,4R,5R)-5-(3-(3-Chloro-phenoxy)-1-methyl-(Z)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-

((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

79. 3-(4-((2S,3R,4R,5R)-5-(3-(3-Chloro-phenoxy)-1-methyl-(Z)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

80. 3-(3-Amino-4-((2S,3R,4R,5R)-5-(3-(2,4-dichloro-phenoxy)-1-methyl-(Z)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

81. 3-(3-Fluoro-4-((2S,4S,5R)-5-(3-((E)-3-fluoro-4-morpholin-4-yl-phenoxy)-1-methyl-(Z)-propenyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

82. 3-(3-Amino-4-((2S,4S,5R)-5-(3-((E)-3-fluoro-4-morpholin-4-yl-phenoxy)-1-methyl-(Z)-propenyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

83. 3-(4-((2S,3R,4S,5R)-3-Amino-5-(1-((E)-3,4-difluoro-benzyloxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

84. 3-(4-((2S,3S,4R,5R)-5-(3-(3-Chloro-phenoxy)-1-methyl-(Z)-propenyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

85. 3-(3-Amino-4-((2S,3S,4R,5R)-5-(3-(4-fluoro-phenoxy)-1-methyl-(Z)-propenyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

86. 3-(4-((2S,3S,4S,5R)-5-(1-((E)-2-Fluoro-benzyloxyimino)-ethyl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

87. 3-(3-Amino-4-((2S,3S,4S,5R)-5-(1-((E)-2-chloro-5-fluoro-benzyloxyimino)-ethyl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

88. 3-(4-((2S,3S,4S,5R)-5-(3-(3-Chloro-phenoxy)-1-methyl-(E)-propenyl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

89. 3-(3-Amino-4-((2S,3S,4S,5R)-5-(3-(2,4-dichloro-phenoxy)-1-methyl-(E)-propenyl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

90. 3-(4-((2S,3S,4S,5R)-5-(3-(2-Fluoro-4-chloro-phenoxy)-1-methyl-(Z)-propenyl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

91. 3-(3-Amino-4-((2S,3S,4S,5R)-5-(3-(3,4-difluoro-phenoxy)-1-methyl-(Z)-propenyl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

92. 3-(4-((2S,4S,5R)-5-(1-((Z)-2-Chloro-benzyloxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

93. 3-(4-((2S,3R,4S,5R)-5-(1-((Z)-2,4-Dichloro-5-fluoro-benzyloxyimino)-ethyl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

94. 3-(4-((2S,3R,4S,5R)-5-(1-((Z)-2-Chloro-benzyloxyimino)-ethyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

95. 3-(4-((2S,4S,5R)-5-(1-((Z)-3,4-Difluoro-benzyloxyimino)-propyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

96. 3-(4-((2S,4S,5R)-5-((Z)-1-Benzyloxyimino-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

97. 3-(4-((2S,3S,4R,5R)-5-(1-((Z)-2-Fluoro-benzyloxyimino)-ethyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

98. 3-(4-((2S,3S,4R,5R)-5-(1-((Z)-2,4-Dichloro-benzyloxyimino)-ethyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

99. 3-(4-((2S,3R,4R,5R)-5-(1-((Z)-2,4-Dichloro-benzyloxyimino)-ethyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

100. 3-(3-Fluoro-4-((2S,4S,5R)-5-(1-((Z)-3-fluoro-4-morpholin-4-yl-benzyloxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

101. 3-(3-Amino-4-((2S,4S,5R)-5-(1-((Z)-2-fluoro-4-chloro-benzyloxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

102. 3-(4-((2S,3R,4R,5R)-5-(1-((Z)-2-Chloro-benzyloxyimino)-ethyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

103. 3-(3-Amino-4-((2S,3R,4R,5R)-5-(1-((Z)-2-chloro-5-fluoro-benzyloxyimino)-ethyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

104. 3-(4-((2S,4S,5R)-5-(1-((Z)-3-Chloro-benzyloxyimino)-propyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

105. 3-(3-Amino-4-((2S,4S,5R)-5-(1-((Z)-3-Chloro-benzyloxyimino)-propyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

106. 3-(4-((2S,3S,4R,5R)-5-(1-((Z)-2-Chloro-benzyloxyimino)-propyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

107. 3-(4-((2S,3S,4R,5R)-5-(1-((Z)-3-Chloro-benzyloxyimino)-propyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

108. 3-(3-Amino-4-((2S,4S,5R)-5-(1-((Z)-3-fluoro-4-morpholin-4-yl-benzyloxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

109. 3-(4-((2S,3S,4R,5R)-5-(1-((Z)-2,4-Dichloro-benzyloxyimino)-ethyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

110. 3-(3-Amino-4-((2S,3S,4R,5R)-5-(1-((Z)-2-fluoro-benzyloxyimino)-ethyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

111. 3-(4-((2S,4S,5R)-5-(1-((E)-3,4-Difluoro-benzyloxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

112. 3-(4-((2S,4R,5R)-5-(1-((E)-3-Chloro-benzyloxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

113. 3-(4-((2S,4R,5R)-5-(3-(2,4-Dichloro-phenoxy)-1-methyl-(E)-propenyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

114. 3-(4-((2S,4R,5R)-5-(1-((E)-3-Chloro-benzyloxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

115. 3-(3-Fluoro-4-((2S,4R,5R)-4-hydroxy-5-(1-((E)-4-morpholin-4-yl-benzyloxyimino)-ethyl)-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

116. 3-(3-Fluoro-4-((2S,4R,5R)-5-(1-((E)-3-fluoro-4-piperidin-1-yl-benzyloxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide

The invention also relates to a pharmaceutical composition for the treatment of a disorder selected from a bacterial infection, a protozoal infection, and disorders related to bacterial infections or protozoal infections, in a mammal, fish, or bird which comprises a therapeutically effective amount of a compound of formula 1, a prodrug thereof or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The invention also relates to a pharmaceutical composition for the treatment of a disorder selected from a bacterial infection, a protozoal infection, and disorders related to bacterial infections or protozoal infections, in a mammal, fish, or bird which comprises a therapeutically effective amount of a compound of formula 1, a prodrug thereof or a pharmaceutically acceptable salt thereof, in combination with a beta-lactam, quinolone, tetracycline, streptogramin, aminoglycoside, glycopeptide, macrolide or oxazolidinone antibiotic; or in combination with a compound which inhibits bacterial or protozoal efflux or degradation of a compound according to formula 1.

The invention also relates to a method of treating a disorder selected from a bacterial infection, a protozoal infection, and disorders related to bacterial infections or protozoal

infections, in a mammal, fish, or bird which comprises administering to said mammal, fish or bird a therapeutically effective amount of a compound of formula 1, a prodrug thereof or a pharmaceutically acceptable salt thereof.

The invention also relates to a method of treating a disorder selected from a bacterial infection, a protozoal infection, and disorders related to bacterial infections or protozoal infections, in a mammal, fish, or bird which comprises administering to said mammal, fish or bird a therapeutically effective amount of a compound of formula 1, a prodrug thereof or a pharmaceutically acceptable salt thereof, in combination or co-administered with a beta-lactam, quinolone, tetracycline, streptogramin, aminoglycoside, glycopeptide, macrolide or oxazolidinone antibiotic; or in combination with a compound which inhibits bacterial or protozoal efflux or degradation of a compound according to formula 1.

The term "treating", as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

As used herein, unless otherwise indicated, the terms or phrases "bacterial infection(s)", "protozoal infection(s)", and "disorders related to bacterial infections or protozoal infections" include the following: pneumonia, otitis media, sinusitus, bronchitis, tonsillitis, and mastoiditis related to infection by *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus, Enterococcus faecalis, E. faecium, E. casselflavus, S. epidermidis, S. haemolyticus,* or *Peptostreptococcus* spp.; pharyngitis, rheumatic fever, and glomerulonephritis related to infection by *Streptococcus pyogenes,* Groups C and G streptococci, *Corynebacterium diphtheriae,* or *Actinobacillus haemolyticum;* respiratory tract infections related to infection by *Mycoplasma pneumoniae, Legionella pneumophila, Streptococcus pneumoniae, Haemophilus influenzae,* or *Chlamydia pneumoniae;* blood and tissue infections, including endocarditis and osteomyelitis, caused by *S. aureus, S. haemolyticus, E. faecalis, E. faecium, E. durans,* including strains resistant to known antibacterials such as, but not limited to, beta-lactams, vancomycin, aminoglycosides, quinolones, chloramphenicol, tetracylines and macrolides; uncomplicated skin and soft tissue infections and abscesses, and puerperal fever related to infection by *Staphylococcus aureus,* coagulase-negative staphylococci (i.e., *S. epidermidis, S. hemolyticus,* etc.), *Streptococcus pyogenes , Streptococcus agalactiae,* Streptococcal groups C-F (minute-colony streptococci), viridans streptococci, *Corynebacterium minutissimum, Clostridium* spp., or *Bartonella henselae;* uncomplicated acute urinary tract infections related to infection by *Staphylococcus aureus,* coagulase-negative staphylococcal species, or *Enterococcus* spp.; urethritis and cervicitis; sexually transmitted diseases related to infection by *Chlamydia trachomatis,*

Haemophilus ducreyi, Treponema pallidum, Ureaplasma urealyticum, or *Neiserria gonorrheae;* toxin diseases related to infection by *S. aureus* (food poisoning and toxic shock syndrome), or Groups A, B, and C streptococci; ulcers related to infection by *Helicobacter pylori;* systemic febrile syndromes related to infection by *Borrelia recurrentis;* Lyme disease related to infection by *Borrelia burgdorferi;* conjunctivitis, keratitis, and dacrocystitis related to infection by *Chlamydia trachomatis, Neisseria gonorrhoeae, S. aureus, S. pneumoniae, S. pyogenes, H. influenzae,* or *Listeria* spp.; disseminated *Mycobacterium avium* complex (MAC) disease related to infection by *Mycobacterium avium,* or *Mycobacterium intracellulare;* infections caused by *Mycobacterium tuberculosis, M. leprae, M. paratuberculosis, M. kansasii,* or *M. chelonei;* gastroenteritis related to infection by *Campylobacter jejuni;* intestinal protozoa related to infection by *Cryptosporidium* spp.; odontogenic infection related to infection by viridans streptococci; persistent cough related to infection by *Bordetella pertussis;* gas gangrene related to infection by *Clostridium perfringens* or *Bacteroides* spp.; and atherosclerosis or cardiovascular disease related to infection by *Helicobacter pylori* or *Chlamydia pneumoniae.* Bacterial infections and protozoal infections, and disorders related to such infections, which may be treated or prevented in animals include the following: bovine respiratory disease related to infection by *P. haemolytica, P. multocida, Mycoplasma bovis,* or *Bordetella* spp.; cow enteric disease related to infection by protozoa (i.e., coccidia, cryptosporidia, etc.); dairy cow mastitis related to infection by *S. aureus, Strep. uberis, Streptococcus agalactiae, Streptococcus dysgalactiae, Corynebacterium,* or *Enterococcus* spp.; swine respiratory disease related to infection by *A. pleuro., P. multocida,* or *Mycoplasma* spp.; swine enteric disease related to infection by *Lawsonia intracellularis, Salmonella,* or *Serpulina hyodysinteriae;* cow footrot related to infection by *Fusobacterium* spp; cow hairy warts related to infection by *Fusobacterium necrophorum* or *Bacteroides nodosus;* cow pink-eye related to infection by *Moraxella bovis;* cow premature abortion related to infection by protozoa (i.e. neosporium); skin and soft tissue infections in dogs and cats related to infection by *S. epidermidis, S. intermedius,* coagulase neg. *Staphylococcus* or *P. multocida;* and dental or mouth infections in dogs and cats related to infection by *Alcaligenes* spp., *Bacteroides* spp., *Clostridium* spp., *Enterobacter* spp., *Eubacterium, Peptostreptococcus, Porphyromonas,* or *Prevotella.* Other bacterial infections and protozoal infections, and disorders related to such infections, which may be treated or prevented in accord with the method of the present invention are referred to in J. P. Sanford et al., "The Sanford Guide To Antimicrobial Therapy," 26th Edition, (Antimicrobial Therapy, Inc., 1996).

The compounds of the present invention may be active against the bacteria and protozoa, and associated conditions, referred to above, or specific strains of the bacteria and protozoa referred to above.

The term "halo", as used herein, unless otherwise indicated, includes fluoro, chloro, bromo or iodo. Preferred halo groups are fluoro and chloro.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, cyclic or branched moieties. It is understood that for said alkyl group to include cyclic moieties it must contain at least three carbon atoms.

The term "alkenyl", as used herein, unless otherwise indicated, includes alkyl groups, as defined above, having at least one carbon-carbon double bond.

The term "alkynyl", as used herein, unless otherwise indicated, includes alkyl groups, as defined above, having at least one carbon-carbon triple bond.

The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl or naphthyl.

The term "4 to 10 membered heterocyclic", as used herein, unless otherwise indicated, includes aromatic and non-aromatic heterocyclic groups containing one or more heteroatoms each selected from O, S and N, wherein each heterocyclic group has from 4 to 10 atoms in its ring system. Non-aromatic heterocyclic groups include groups having only 4 atoms in their ring system, but aromatic heterocyclic groups must have at least 5 atoms in their ring system. The heterocyclic groups include benzo-fused ring systems and ring systems substituted with one or more oxo moieties. An example of a 4 membered heterocyclic group is azetidinyl (derived from azetidine). An example of a 5 membered heterocyclic group is thiazolyl and an example of a 10 membered heterocyclic group is quinolinyl. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl and quinolizinyl. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. The foregoing groups, as derived from the compounds listed above, may be C-attached or N-attached where such is possible. For instance, a group derived from pyrrole may be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached). The terms "5 to 12 membered

heterocyclic", "5 to 6 membered heterocyclic", and other uses of "heterocyclic", correspond to the above definition with an appropriate number of ring members.

The phrase "pharmaceutically acceptable salt(s)", as used herein, unless otherwise indicated, includes salts of acidic or basic groups which may be present in the compounds of the present invention. The compounds of the present invention that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds of are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, acid citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts. The compounds of the present invention that include a basic moiety, such as an amino group, may form pharmaceutically acceptable salts with various amino acids, in addition to the acids mentioned above.

Those compounds of the present invention that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline earth metal salts and, particularly, the calcium, magnesium, sodium and potassium salts of the compounds of the present invention.

The compounds of the present invention have asymmetric centers and therefore exist in different enantiomeric and diastereomeric forms. This invention relates to the use of all optical isomers and stereoisomers of the compounds of the present invention, and mixtures thereof, and to all pharmaceutical compositions and methods of treatment that may employ or contain them. In this regard, the invention includes both the E and Z configurations of the $-OR^3$ group connected to the nitrogen where R^1 and R^2 are taken together as an oxime moiety of the formula $=N-OR^3$. The invention also includes both E and Z configurations of the R^5 and X^1-X^2-R^6 groups connected to cargon where R^1 and R^2 are taken together as $=C(R^5)X^1-X^2-R^6$. The compounds of formula 1 may also exist as tautomers. This invention relates to the use of all such tautomers and mixtures thereof.

The subject invention also includes isotopically-labelled compounds, and the pharmaceutically acceptable salts thereof, which are identical to those recited in formula 1, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^2H, ^3H, ^{13}C,

^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labelled compounds of formula 1 of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples and Preparations below, by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

This invention also encompasses pharmaceutical compositions containing and methods of treating bacterial infections through administering prodrugs of compounds of the formula 1. Compounds of formula 1 having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues is covalently joined through an amide or ester bond to a free amino, hydroxy or carboxylic acid group of compounds of formula 1. The amino acid residues include but are not limited to the 20 naturally occurring amino acids commonly designated by three letter symbols and also includes 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline homocysteine, homoserine, ornithine and methionine sulfone. Additional types of prodrugs are also encompassed. For instance, free carboxyl groups can be derivatized as amides or alkyl esters. Free hydroxy groups may be derivatized using groups including but not limited to hemisuccinates, phosphate esters, dimethylaminoacetates, and phosphoryloxymethyloxycarbonyls, as outlined in *Advanced Drug Delivery Reviews*, **1996**, *19*, 115. Carbamate prodrugs of hydroxy and amino groups are also included, as are carbonate prodrugs, sulfonate esters and sulfate esters of hydroxy groups. Derivatization of hydroxy groups as (acyloxy)methyl and (acyloxy)ethyl ethers wherein the acyl group may be an alkyl ester, optionally substituted with groups including but not limited to ether, amine and carboxylic acid functionalities, or where the acyl group is an amino acid ester as described above, are also encompassed. Prodrugs of this type are described in *J. Med. Chem.* **1996**, *39*, 10. Free amines can also be derivatized as amides, sulfonamides or phosphonamides. All of these prodrug

moieties may incorporate groups including but not limited to ether, amine and carboxylic acid functionalities.

Selective introduction of prodrug side chains can be carried out on the hydroxy groups of the hygromycin A core molecule. For instance, exhaustive silylation of the six hydroxy groups of hygromycin A can be carried out, for instance with tert-butyl dimethylsilyl chloride. Subjection of the hexasilyl derivative to the action of potassium carbonate in methanol at room temperature selectively removes the phenolic silyl group, allowing further selective modification at that position. In another example, incomplete silylation of hygromycin A provides the pentasilyl derivative in which the C-2" hydroxy group of the furanose ring is free. Selective acylation, alkylation, etc. can be carried out on this derivative to provide prodrug attachment at C-2", followed by elaboration to the compounds of formula 1.

Selective introduction of prodrug side chains onto the Fragment C moiety may be carried out by functionalizing Fragment C (Scheme 1) prior to coupling with fragments B and A, or by utilizing selective protection strategies after assembly of the three fragments.

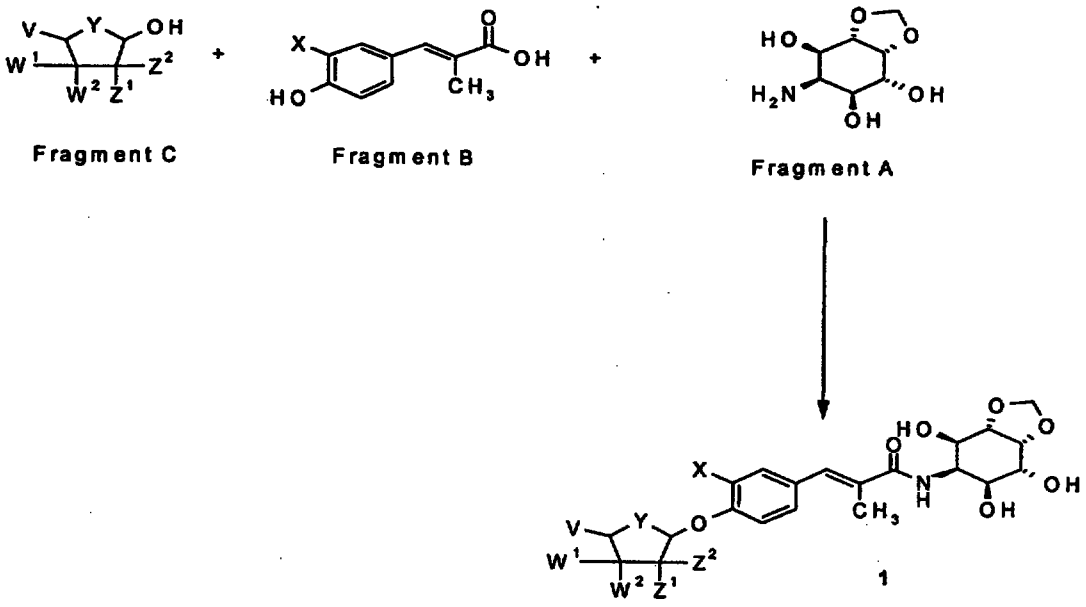
Selective introduction of prodrug side chains onto the hydroxyl groups of the inositol sugar can be carried out through total synthesis of the inositol (Fragment A in Scheme 1). Adaptation of the chemistry published by Chida (*J. Org. Chem.*, **1991**, *56*, 2976), Arjona (*Tetrahedron Lett.*, **1995**, *36*, 1319 and Dudash (Dissertation, Stanford Univ., 1998, Diss. Abstr. Int., B, **1998**, *59*, 2754) allows selective addition of a prodrug onto the hydroxyl group of choice through use of selectively protected intermediates described in these reports. The inositol derivative bearing the prodrug is then appended to fragments B and C as described below.

Detailed Description of the Invention

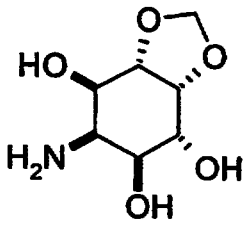
The preparation of the compounds of the present invention is described and illustrated below.

Preparation of the compounds of formula 1 can most flexibly be carried out through assembly of Fragments A, B and C as outlined below. Alternatively, many of the compounds of formula 1 can be prepared from the natural product hygromycin A, as described in later sections. In the procedures provided below, certain abbreviations well known to those skilled in the art are used. For instance, "h" refers to hour(s), "min" refers to minute(s), and "rt" refers to room temperature.

Scheme 1



Preparation of Fragment A



2

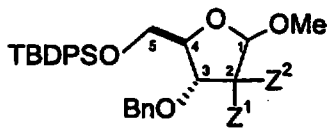
(1aS,3aR,4R,5S,6R,7R)-6-Amino-hexahydro-benzo[1,3]dioxole-4,5,7-triol can be prepared from hygromycin A (*Agric. Biol. Chem.* **1978**, *42*, 279 or *J. Org. Chem.* **1991**, *56*, 2976) with the former being the preferred method.

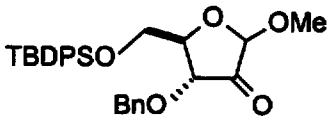
Preparation of Fragment C

In the following description, compounds may contain R^3, R^{12} or R^{13} groups that may not be compatible with functionalization of C-2, C-3 or C-4. Functional groups within R^3, R^{12} or R^{13} that are not compatible with chemistry carried out at C-2, C-3 or C-4, or during subsequent chemistry, can be protected prior to C-2, C-3 or C-4 manipulation. For example, an alcohol might be protected as an ether (benzyl, allyl or silyl) or ester (benzoate, pivaloate or acetate) and subsequently deprotected at an appropriate time. If Z^1 and Z^2 are taken together to form a ketone (as in compound 4), or an R^3, R^{12} or R^{13} within Z^1, Z^2, W^1 or W^2 contains a ketone, it may be necessary to protect it, for instance as a dimethyl ketal through the use of methanol and catalytic acid such as camphorsulfonic acid or p-toluenesulfonic acid (p-TsOH). Deprotection of the ketal can be carried out concomitantly with the cleavage of the

anomeric methyl acetal to generate the hydroxyl group at C-1. Alternatively, a ketone may be masked as its protected alcohol, which can then be regenerated by deprotection and oxidation, for example under Swern conditions (*J. Org. Chem.*, **1976**, *41*, 3329). An amine might be protected as its 9-fluorenylmethoxycarbonyl- (FMOC), benzyloxycarbonyl- (CBZ) or tert-butoxycarbonyl carbamate (BOC) (see *Protective Groups in Organic Synthesis*, T. Greene and P. Wuts, Ed., John Wiley & Sons Ltd., New York, 1991 or *Protecting Groups*, P. Kocienski, Ed., Thieme Medical Publishers, New York, 1994) and subsequently deprotected at an appropriate time. It might also be advantageous to introduce said groups at a later stage by utilizing an intermediate that may, at an appropriate time, be further elaborated to the desired R^3, R^{12} or R^{13}. Acids, carbonyl-linked amides and esters may be generated after C-2, C-3 or C-4 elaboration from a protected primary alcohol, which is unmasked by deprotection and elaborated by double oxidation, for example Swern conditions followed by action of potassium permanganate (*Tetrahedron Lett.*, **1986**, *27*, 4537 and *J. Am. Chem. Soc.*, **1987**, *109*, 7575), or sodium chlorite (*J. Org. Chem.*, **1986**, *51*, 567 and *J. Am. Chem. Soc.*, **1997**, *119*, 7974) to the carboxylic acid. This may then coupled with the appropriate alcohol or amine, for instance by the action of dicyclohexylcarbodiimide (DCC), to produce the desired ester or amide. An N-linked amide or sulfonamide may be carried through as an amine, protected as above, which is then deprotected and acylated or sulfonylated. N-linked amides and sulfonamides and amines may alternatively be introduced by displacement of a leaving group. For example, a protected alcohol may be deprotected and the resulting alcohol transformed into the mesylate, for instance through the action of methanesulfonyl chloride and triethylamine (NEt_3) (*J. Org. Chem.*, **1970**, *35*, 3195). The mesylate is then displaced by azide, for example using sodium azide in N,N-dimethylformamide (DMF) and the azide reduced to the primary amine using for instance triphenylphosphine followed by aqueous hydrolysis. Acylation may then provide the corresponding amide. Sulfur containing moieties may also be introduced in this fashion, for example, by the displacement of the aforementioned mesylate with the appropriate thiolate or protected thiolate, followed if necessary by oxidation of the sulfur to the sulfoxide or sulfone.

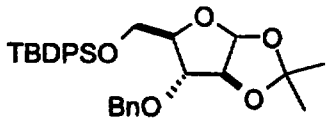
Fragment C can be prepared by first functionalizing at the C-2 and C-3 positions, followed by elaboration of the substituent at C-4. Functionalization of the C-2 position may be carried out first, as described below, to generate intermediate **3** (TBDPS = tert-butyldiphenylsilyl), where Z^1 and Z^2 are as described in formula **1**, or are present as a precursor, protected precursor or protected form of Z^1 and Z^2.





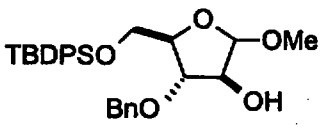
3 4

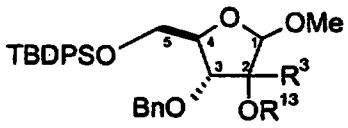
Compound **4** (Bn = benzyl), where Z^1 and Z^2 are taken together to form =O may be prepared from available starting material **5** (*Tetrahedron*, **1995**, *51*, 871).

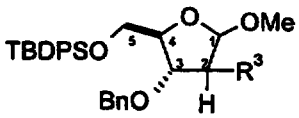


5

For instance, selective removal of the 1, 2-acetonide and methyl ketal formation may be achieved with the action of trifluoroacetic acid (TFA) in tetrahydrofuran/methanol (see precedent: *J. Org. Chem.*, **1986**, *51*, 789) or alternatively by a two step procedure. For example, acetal cleavage may be achieved with the action of TFA in tetrahydrofuran/water (*J. Org. Chem.*, **1986**, *51*, 789) followed by ketal formation using methanol in the presence of acid (*J. Am. Chem. Soc.*, **1954**, *76*, 3598 and *J. Org. Chem.*, **1984**, *49*, 4564). The resulting methyl ketal, **6**, may be oxidized, for example under Swern (*J. Org. Chem.*, **1976**, *41*, 3329) or Dess-Martin (*J. Org. Chem.*, **1983**, *48*, 4155) conditions, to lead to compound **4**.







6 **7** **8**

Compounds **7** and **8** may be prepared from either **6** or **4**.

For example, compound **7**, with R^{13} = H and R^3 as defined but not H, may be prepared by addition of an organometallic reagent R^3M, for example Grignard, organolithium or organocerium reagents (*Tetrahedron Lett.*, **1984** *25*, 4233) to **4** in a solvent such as tetrahydrofuran (THF), dioxane or Et_2O at a temperature ranging from -78°C to 25°C. These reagents may be prepared from the corresponding halide, R^3-halide, using standard procedures (see *Organometallics In Synthesis; A Manual*, M. Schlosser, Ed., John Wiley & Sons Ltd., New York, 1994). This addition will generate both C-2 diastereomers, which may be separated using chromatography.

Compound **7** with R^{13} as defined and R^3 = H may be prepared from **6** by reaction of the alkoxide of **6**, generated with a strong base such as sodium hydride or potassium

carbonate, with halide-R^3 in a polar aprotic solvent, such as THF or DMF at a temperature ranging from 0°C to 25°C To generate the α-OR^3 one may first react **6** in a Mitsunobu reaction with dialkylazodicarboxylate, wherein the alkyl group is preferably ethyl, propyl, isopropyl, or tert-butyl; 4-nitrobenzoic acid and triphenylphosphine in a suitable organic solvent such as THF, Et_20 or dioxane at a temperature ranging from 0°C to 65°C, preferably from 0°C to 25°C (*Bull. Chem. Soc. Jpn.*, **1967**, *40*, 2380). Hydrolysis of the resultant ester, with an alkali base such as lithium hydroxide or sodium hydroxide, in a solvent mixture containing water, methanol and tetrahydrofuran at a temperature ranging from 0°C to 25°C, will lead to the desired 2-α-OH diastereomer which may be subsequently alkylated as above.

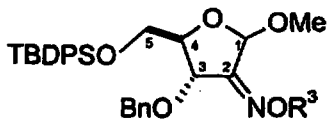
Compound **7**, with R^{13} as defined but not H and R^3 as defined but not H, may be prepared by further reaction of compound **7** wherein R^{13} is as defined and R^3 is H, prepared as described above. The 2-OH may be alkylated by reaction of the alkoxide, generated with a strong base such as sodium hydride or potassium carbonate, with halide-R^3 in a polar aprotic solvent, such as tetrahydrofuran or dimethylformamide at a temperature ranging from 0°C to 25°C.

Compound **8** may be prepared by organometallic addition, for example Grignard or organocerium addition (*Tetrahedron Lett.*, **1984** 25, 4233) of the appropriate R^3 reagent to **4**. The resulting mixture of diastereomers may be separated and the C-2-OH removed by Barton-McCombie deoxygenation (*J. Chem. Soc. Perkin I*, **1975**, 1574). Compound **8** may also be prepared by addition of said organometallic to the C-2-iodide formed from **6** in an aprotic solvent, such as ethyl ether or tetrahydrofuran, at temperatures from -78°C to 0°C, preferably from -78°C to -25°C. The aforementioned iodide may be formed by reaction of **6** with iodine, imidazole and triphenylphosphine in a solvent such as toluene at a temperature ranging from 0°C to 25°C (*J. Am. Chem. Soc.*, **1998**, *120*, 7647).

Compound **8**, where R^3 is $-CH_2O-X$ and X falls under the definition of R^3, may alternatively be prepared from **4** via formation of the C-2-methylene (i.e. Z^1 and Z^2 are taken together to form $=CH_2$), which may be accomplished following the precedent in *J. Org. Chem.*, **1995**, *60*, 7298, followed by hydroboration (*Org. React.*, **1963**, *13*, 1 and *Tetrahedron*, **1981**, *37*, 3547) and finally alkylation, as above

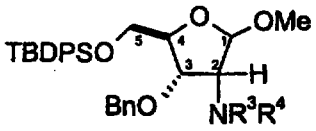
Compound **8**, where R^3 is H, may be prepared from Barton-McCombie deoxygenation (*J. Chem. Soc. Perkin I*, **1975**, 1574) of **6**. Alternatively, **8** may be prepared from commercially available 1-O-methyl-2-deoxy-D-ribose. For example, selective silylation with tert-butyl diphenylsilyl chloride (TBDPSCl) of the C-5-OH may be accomplished by reaction of the ribose in a solvent such as DMF or dichloromethane with tert-butyl diphenylsilyl chloride in the presence of an amine base, such as pyridine or triethylamine at a temperature ranging

from 0°C to 25°C. The addition of catalytic dimethylaminopyridine may be advantageous. Benzylation of C-3 OH may be accomplished by subsequent reaction of the C-3-alkoxide, generated by the action of a strong base such as potassium tert-butoxide or sodium hydride, in a solvent such as DMF or THF with benzyl bromide.



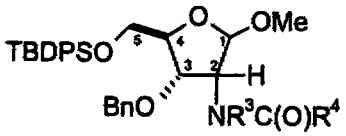
9

Compound **9**, where Z^1 and Z^2 are taken together to form an oxime of the formula $=NOR^3$, wherein R^3 is as defined above, may be prepared by treating compound **4** with a hydroxylamine of the formula R^3ONH_2, using the free base or salt of the hydroxylamine, preferably the free base of the hydroxylamine. The reaction is carried out in an inert solvent, such as methanol, with addition of base, such as K_2CO_3, if the salt, for instance the HCl salt, of the hydroxylamine is used, at a temperature ranging from about 0°C to 65°C, preferably from 0°C to 25°C. The hydroxylamine of formula R^3ONH_2 may be prepared using one or more procedures disclosed in *Bioconj. Chem.*, **1990**, *2*, 96, *J. Pharm. Sci.*, **1969**, *58*, 138 or *Chem. Pharm. Bull.*, **1967**, *15*, 345.



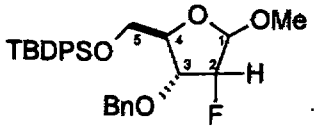
10

Compound **10**, where Z^1 is H and Z^2 is NR^3R^4, wherein R^3 and R^4 are as defined above, may be synthesized by reductive amination at the C-2 ketone site of the compound of formula **4**. Combination of R^4NH_2 and the compound of formula **4** in an inert solvent such as methanol or ethanol and treatment with a reducing agent such as sodium borohydride ($NaBH_4$), sodium triacetoxyborohydride ($NaBH(OAc)_3$), or sodium cyanoborohydride ($NaCNBH_3$) at a temperature ranging from 0°C to 25°C provides the product with R^3 = H. To introduce R^3 groups wherein R^3 is RCH_2- or RR'CH-, and R' and R are any of the moieties in the definition of R^3 that may be attached through a methylene or methine group, a reductive alkylation can be carried out with an appropriate aldehyde or ketone of the formula RC(O)H or RC(O)R' as described above. An Eschweiler-Clark reaction may be used to introduce a methyl group as the R^3 substituent (*Org. React.*, **1949**, *5*, 301). Both C-2 diastereomers are available using this chemistry.



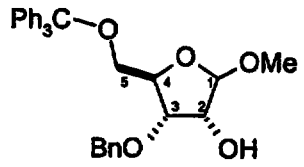
11

To provide an amide group such as in compound **11**, where Z^1 is H and Z^2 is $NR^3C(O)R^4$, an amine of the formula $-NHR^3$ may be introduced as described above and then an acyl moiety of the formula $-C(O)R^4$ may be introduced by treating the intermediate with an activated form of the carboxylic acid, such as R^4COCl or $R^4C(O)OC(O)R^4$, or by using an amide coupling agent such as 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), 1,1'-carbonyl-diimidazole (CDI), or a carbodiimide such as DCC in a solvent such as dichloromethane, DMF or chloroform at a temperature ranging from 0°C to 25°C. Both C-2 diastereomers are available using this chemistry. Compounds of formula **11** wherein R^3 is H and R^4 is as defined above, may be prepared through use of the primary amine derived from reductive amination of the compound of formula **4** with an ammonia equivalent, for instance through the use of ammonium acetate and sodium cyanoborohydride or sodium triacetoxyborohydride. Alternatively, this primary amine can be prepared via the corresponding azide: (1) the C-2 alcohol of compound **6** is transformed into the mesylate, for instance through the action of methanesulfonyl chloride and triethylamine in a solvent such as dichloromethane at a temperature ranging from 0°C to 25°C; 2) the mesylate is displaced by azide, for example using sodium azide in DMF at a temperature ranging from 0°C to 90°C, preferably from 60°C to 90°C; and 3) the azide is reduced to the primary amine using for instance triphenylphosphine at a temperature from 25°C to 60°C, followed by aqueous hydrolysis. Reaction of the resultant primary amine with an activated form of $R^4C(O)OH$, for instance $R^4C(O)Cl$ or $R^4C(O)OC(O)R^4$, provides the corresponding amide. Alternatively, amide coupling reagents can be used with $R^4C(O)OH$, such as 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide (EDC), diethyl phosphoryl cyanide (DEPC), DCC, CDI or EEDQ. To incorporate an R^3 group other than H, the amide referred to above may be alkylated. The alkylation may be carried out with a base and an alkylating agent, such as sodium hydride and an appropriate bromide of the formula R^3-Br.



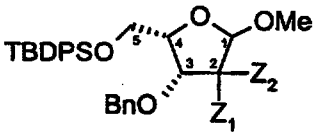
12

Compound **12** may be prepared from available starting material **13** (*Chem. Ber.* **1979**, *112*, 1689).



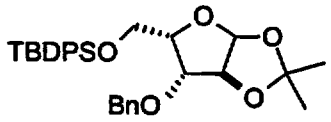
13

For instance, diethylaminosulfur trifluoride (DAST) reaction of **13** in a solvent such as dichloromethane or THF at a temperature ranging from 0°C to 65°C (*Tetrahedron Lett.*, **1991**, *32*, 5963) provides the C-2-F intermediate. Removal of the trityl group using mild acid, for example p-toluenesulfonic acid in MeOH (*Tetrahedron Lett.*, **1981**, *22*, 1299), followed by silylation of the resultant primary alcohol with TBDPS-Cl, for example in dichloromethane or DMF in the presence of an amine base such as triethylamine at a temperature ranging from 0°C to 25°C, may be used to complete the preparation of **12**. The other C-2 diastereomer may be obtained by first inverting the C-2-OH of **13** by Mitsunobu inversion as described previously for compound **6**.

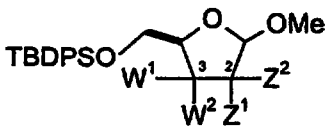


14

Compound **14** may be prepared from the C-4 isomer **15** (*J. Am. Chem. Soc.*, **1987**, *109*, 2205), using chemistry described for the preparation of compound **3**.

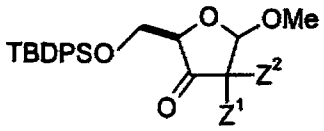


15



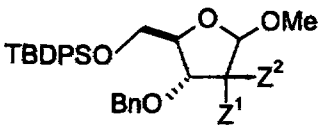
16

Functionalization of the C-3 position can be carried out on the substrates described above, such that the desired moieties are installed at both the C-2 and C-3 positions to generate intermediate **16**, where W^1, W^2, Z^1 and Z^2 are as described in formula **1**, or are present as their precursors, protected precursors, or protected derivatives.



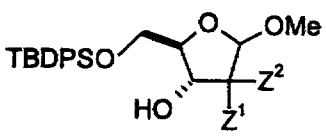
17

Compound **17** may be prepared from compound **3**.

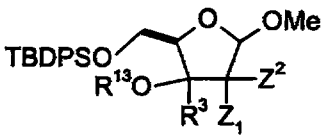


3

Removal of the benzyl group from **3** can be carried out by hydrogenation, for instance with hydrogen gas and a catalyst such as palladium on carbon, or by use of a hydrogen transfer agent such as cyclohexadiene and palladium on carbon, in a solvent such as THF, dioxane or methanol at a temperature ranging from 0°C to 25°C to provide alcohol **18**. Oxidation of **18** by the methods cited for conversion of **6** to **4** generates **17**.

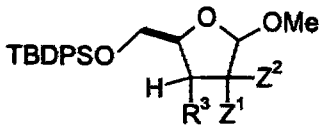


18



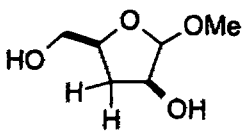
19

Compound **19** can be prepared from **17** and **18** using the chemistry described for synthesis of compound **7**.

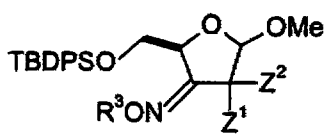


20

Compound **20** can be prepared from **17** using the chemistry described for synthesis of compound **8**. Compound **20** wherein R^3 is H can be alternatively derived from known starting material **21** (*Acta Chem. Scand., Ser. B.*, **1981**, *35*, 155) by protection of the primary alcohol as its TBDPS ether as described for compound **8**, and elaboration of the hydroxy group at C-2 as described for compounds **4**, **7**, **8**, **9**, **10**, **11**, and **12** above.

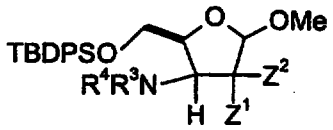


21



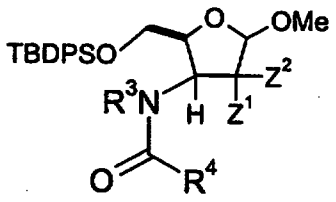
22

Compound **22** can be synthesized from **17** as described for preparation of compound **9**.



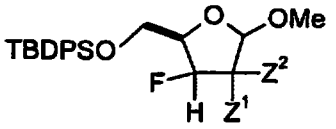
23

Compound **23** can be prepared from compound **17** as described for **10**.



24

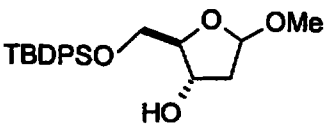
Compound **24** can be prepared from **17** or **18** using the chemistry described for **11**.



25

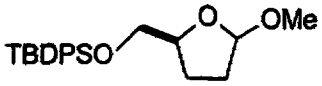
Compound **25** can be prepared from **3** through removal of the TBDPS ether, for instance with a fluoride source such as tetra-n-butyl ammonium fluoride (TBAF) in a solvent such as THF at a temperature ranging from 0°C to 25°C, and installation of a trityl protecting group on the primary alcohol through use of, for instance, trityl chloride and pyridine in dichloromethane at a temperature ranging from 0°C to 25°C. Debenzylation as described for conversion of **3** to **18** is then followed by the elaboration described for compound **12** above.

Where Z^1 is H and Z^2 is H, compound **16** can also be prepared by elaboration of **26**, available from tert-butyldiphenylsilyl ether formation on the primary alcohol of the commercially available diol, by carrying out the chemistry described above.

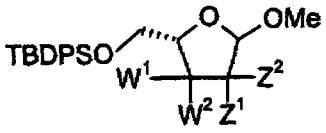


26

Compound **27**, where W^1, W^2, Z^1 and Z^2 are each H in compound **16**, is available from a literature procedure (*J. Org. Chem.*, **1997**, *62*, 1501).



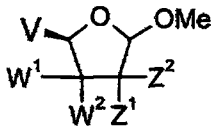
27



28

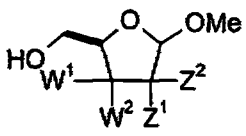
Compound **28**, wherein the substituent at the C-4 position is in the α-orientation, can be prepared from **14**, using the chemistry described above for its isomer **3**.

At this stage, the tert-butyldiphenylsilyloxymethyl substituent at the C-4 position of intermediates **16** can be modified to provide key intermediates for introduction of V, as defined in the compound of formula **1**. These compounds are then used to prepare **29**, wherein V is as described in the compound of formula **1**.

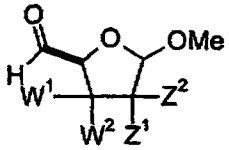


29

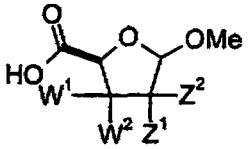
Removal of the tert-butyldiphenylsilyl protecting group from **16** can be carried out by treatment with a fluoride source such as TBAF in a solvent such as THF at a temperature ranging from 0°C to 25°C, to provide primary alcohol **30**. Swern or Dess-Martin oxidation of **30** gives aldehyde **31**, which can be further oxidized through the action of potassium permanganate (*Tetrahedron Lett.*, **1986**, *27*, 4537 and *J. Am. Chem. Soc.*, **1987**, *109*, 7575) or sodium chlorite (*J. Org. Chem.* **1989**, *54*, 4100) to provide carboxylic acid **32**.



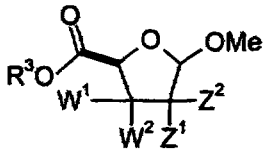
30



31

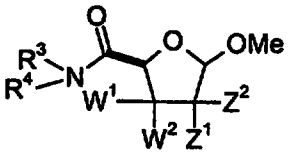


32

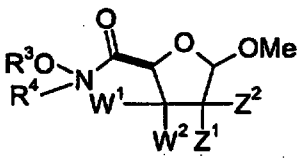


33

Compound **33** can be prepared from compound **32** through esterification with alcohol R^3OH. Reaction of R^3OH and **32** in the presence of a coupling agent such as EDC, DEPC, DCC, CDI or EEDQ in a solvent such as dichloromethane, DMF or chloroform at a temperature ranging from 0°C to 25°C provides compound **33**.



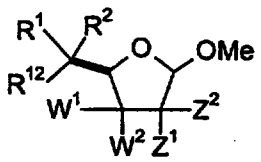
34



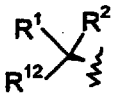
35

Compounds **34** and **35** can be prepared from compound **32** through amide formation with amine R^3R^4NH or hydroxylamine $(R^3O)R^4NH$. Reaction of R^3R^4NH or $(R^3O)R^4NH$ and **32** in the presence of coupling agent such as EDC, DEPC, DCC, CDI or EEDQ in a solvent such as dichloromethane, DMF or chloroform at a temperature ranging from 0°C to 25°C, yields compounds **34** and **35**.

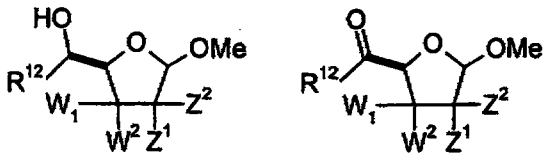
Alternatively, **34** and **35** may be synthesized through reaction of R^3NH_2 or R^3ONH_2 with **32** in the presence of a coupling agent such as EDC, DEPC, DCC, CDI or EEDQ in a solvent such as dichloromethane, DMF or chloroform at a temperature ranging from 0°C to 25°C to generate an amide or hydroxamate. For compounds where R^4 does not equal H, R^4 may then be introduced via reaction of this intermediate amide or hydroxamate with a base such as sodium hydride or potassium t-butoxide and an alkylating agent R^4-L in a solvent such as THF or dioxane at a temperature ranging from 0°C to 65°C, wherein L is a leaving group such as bromide, iodide or mesylate.



36

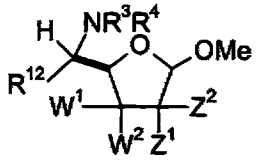
Compound **36**, where V =  , may be prepared from **30**, **31** and **32**.

R^{12}, where R^{12} is not equal to H, can be introduced through organometallic addition of the appropriate R^{12} moiety to aldehyde **31**, providing alcohol **37**, through use of for example the Grignard, organolithium or organocerium reagent (*Tetrahedron Lett.*, **1984** 25, 4233). These reagents may be prepared from the corresponding halide, R^{12}-halide, using standard procedures (see *Organometallics In Synthesis; A Manual*, M. Schlosser, Ed., John Wiley & Sons Ltd., New York, 1994). This addition will generate both C-5 diastereomers, which may be separated using chromatography.



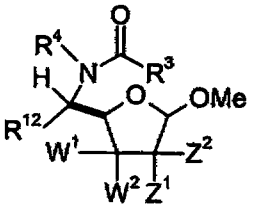
37 38

Ketone **38** is available through Swern or Dess-Martin oxidation of **37**. Alternatively, carboxylic acid **32** can be transformed to its Weinreb amide through reaction with N,O-dimethylhydroxylamine and DCC or CDI in a solvent such as dichloromethane at a temperature ranging from 0°C to 25°C(*Tetrahedron Lett.*, **1981**, *22*, 39). Reaction of the Weinreb amide with an organometallic reagent derived from halide-R^{12}, as described above, also generates **38**.



39

Compound **39** can be synthesized by reductive amination at the ketone functionality of compound **38**. Combination of R^4NH_2 and **38** in an inert solvent and treatment with a reducing agent such as $NaBH_4$, $NaBH(OAc)_3$ or $NaCNBH_3$ provides the product with R^3 = H. To introduce R^3 groups wherein R^3 is RCH_2- or RR'CH-, and R' and R are any of the moieties in the definition of R^3 that may be attached through a methylene or methine group, a reductive alkylation can be carried out with an appropriate aldehyde or ketone of the formula RC(O)H or RC(O)R'. An Eschweiler-Clark reaction may be used to introduce a methyl group as the R^3 substituent. If R^{12} = H, these compounds may be prepared from compound **31** in similar fashion.

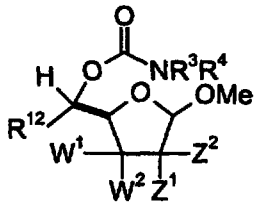


40

For preparation of compounds **40**, an amine of the formula -NHR^4 may be introduced as described above and then an acyl moiety of the formula -$C(O)R^3$ may be introduced by treating the amine intermediate with an activated form of the carboxylic acid, such as R^3COCl or $R^3C(O)OC(O)R^3$, or by reacting the amine intermediate with a carboxylic acid R^3COOH and an amide coupling agent such as EDC, DEPC, DCC, CDI or EEDQ in a solvent such as

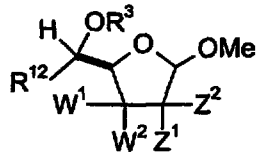
dichloromethane DMF or chloroform at a temperature ranging from 0°C to 25°C. Alternatively, compounds **40**, wherein R^4 is H and R^3 is as defined above, may be prepared through use of the primary amine derived from reductive amination of **38** with an ammonia equivalent, for instance through the use of ammonium acetate and sodium cyanoborohydride or sodium triacetoxyborohydride. This primary amine can also be prepared via the corresponding azide: alcohol **37** can be transformed into the mesylate, for instance through the action of methanesulfonyl chloride and triethylamine; the mesylate is displaced by azide, for example using sodium azide in N,N-dimethylformamide (DMF); and the azide is reduced to the primary amine, using for instance triphenylphosphine followed by aqueous hydrolysis.

Reaction of the primary amine with an activated form of $R^3C(O)OH$, for instance $R^3C(O)Cl$ or $R^3C(O)OC(O)R^3$, provides the corresponding amide. Alternatively, amide coupling reagents , such as EDC, DEPC, DCC, CDI or EEDQ in a solvent such as dichloromethane DMF or chloroform can be used with $R^3C(O)OH$ at a temperature ranging from 0°C to 25°C. To incorporate an R^4 group other than H, the amide referred to above may be alkylated. The alkylation may be carried out with a base and an alkylating agent, such as sodium hydride and an appropriate bromide of the formula R^4-Br. If R^{12} is H, compounds **40** may be prepared from either compound **30** or **31**.



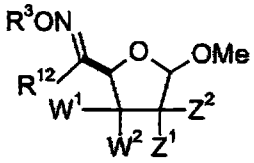
41

Compounds **41** may be prepared by reacting compound **37** with isocyanate R^3NCO in toluene at temperatures from 40°C to 110°C, preferably 50 - 80°C. Addition of 4-dimethylaminopyridine and triethylamine to the reaction may be advantageous. The product of this reaction, which has R^4 equal to H, may be alkylated to give R^4 equal to C_1 - C_{10} alkyl through use of a base such as sodium hydride and an alkylating agent such as a bromide of the formula R^4-Br in a solvent such as THF or dioxane at a temperature ranging from 0°C to 65°C. If R^{12} = H, compounds **41** may be prepared from compound **30**.



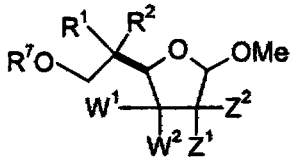
42

Compounds **42** can be prepared through alkylation of compound **37** with R^3-L, wherein L is a leaving group such as Cl, Br or methanesulfonate, in the presence of a base, such as sodium hydride or potassium *tert*-butoxide in a solvent such as THF or dioxane at a temperature ranging from 0°C to 65°C. Compounds of formula **42** where R^3 is an aromatic or heterocyclic moiety may be prepared via a Mitsunobu reaction, wherein compound **37** is subjected to reaction with R^3OH, mediated by triphenylphosphine and diethyl azodicarboxylate (D.L. Hughes, *Org. Reactions*, **1992**, *42*, 335). Alternatively, wherein R^3 is an aromatic or heterocyclic moiety, the alcohol of **37** can be transformed into a leaving group, for instance the bromide or mesylate derivative. The leaving group can then be displaced by R^3OH using a base such as sodium hydride, potassium *tert*-butoxide or potassium carbonate in a solvent such as THF or dioxane at a temperature ranging from 0°C to 65°C. If R^{12} = H, compounds **42** may be prepared from compound **30**.



43

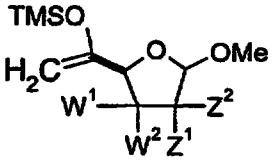
Compounds **43** wherein R^{12} is not H can be prepared by treating ketone **38** with a hydroxylamine of the formula R^3ONH_2, using the same conditions described for the preparation of **9**. If R^{12} = H, compounds **43** may be prepared in the same manner from compound **31**.



44

Compound **44**, where R^{12} can be written as R^7OCH_2, can be prepared from compound **38** where R^{12} = Me, through reaction with triethylamine and trimethylsilyl triflate (TMSOTf) in an aprotic solvent, preferably dichloromethane, at temperatures between -40 °C and 0 °C, preferably -30 °C to -15 °C, to generate enol ether **45**. Reaction of compound **45** with m-chloroperbenzoic acid (mCPBA), in a solvent such as dichloromethane or chloroform at temperatures between 10 °C and 40 °C, followed by an acidic workup, using for instance 0.2 N HCl in THF or dioxane at temperatures between 10 °C and 40 °C, yields α-hydroxy ketone **46**. Alkylation of the hydroxyl group in **46** with a base such as sodium hydride or potassium t-butoxide and halide-R^7, where halide is Br or I, in a solvent such as THF or dimethylsulfoxide

(DMSO) at temperatures between 10 °C and 40 °C, provides compound **47**. For aromatic and heteroaromatic R^7, a Mitsunobu reaction may be carried out with R^7-OH, triphenylphosphine and dialkyl azodicarboxylate. Alternatively, the hydroxyl group of **46** can be converted into a leaving group such as the mesylate and displaced with R^7-OH, under the influence of a base such as sodium hydride or potassium t-butoxide; this reaction can be carried out in an aprotic solvent such as THF or dioxane at temperatures ranging from 20°C to 50°C. Further manipulation, as described above for **38**, generates compound **44**. Alternatively, the carbonyl at C-5 of **46** may be protected, for instance as its dioxolanyl ketal, and R^7 introduced, followed by deprotection and introduction of R^1 and R^2. In another route, protection of the primary alcohol at the 6-position of **46**, for instance as its tert-butyl dimethyl silyl ether or acetate, can be followed by introduction of R^1 and R^2, followed by regeneration of the primary alcohol and introduction of R^7.



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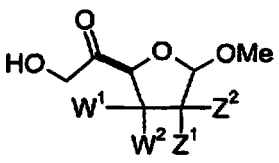
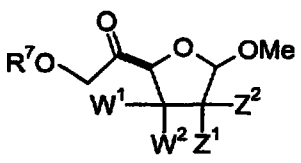


46



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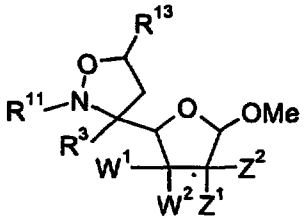
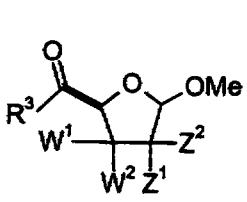
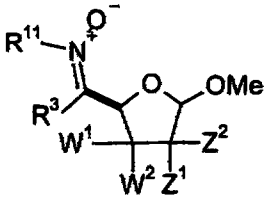


48

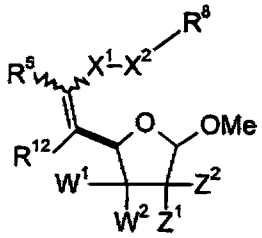
Compound **48** can be prepared from aldehyde **31** through organometallic addition of R^3-M followed by oxidation, as described for R^{12} in preparation of **36**, to give **49**. Reaction of compound **49** with R^{11}-NHOH provides nitrone **50**. The reaction is carried out in an inert solvent, such as methanol, ethanol or pyridine, with addition of base, such as NaOAc, Na_2CO_3 or K_2CO_3, if the salt, for instance the HCl salt, of the hydroxylamine is used, at a temperature ranging from about 0°C to 65°C, preferably from 0°C to 25°C. Cycloaddition with R^{13}-HC=CH_2 provides compound **48**. The cycloaddition reaction is carried out in an inert solvent such as benzene or toluene, at a temperature ranging from 50°C to 110°C, preferably from 80°C to 110°C.



49



50



51

Compounds **51** can be prepared from ketone **38** utilizing the Wittig (*Chem. Rev.*, **1989**, *89*, 863 and *Chem. Soc. Rev.*, **1988**, *17*, 1), Horner-Wadsworth-Emmons (*J. Am. Chem. Soc.*, **1961**, *83*, 1733 and *Chem. Rev.*, **1974**, *79*, 87) or Peterson olefination (*Org. React.*, **1990**, *38*, 1) reactions via reaction with Ph_3P-$CH(R^5)X^1$-X^2-R^8, $(EtO)_2P(O)$-$CH(R^5)X^1$-X^2-R^8 or $(CH_3)_3Si$-$CH(R^5)X^1$-X^2-R^8, respectively. These reagents are generally commercially available but may be alternatively prepared by those skilled in the art. For example, Wittig reagents may be prepared from L-$CH(R^5)X^1$-X^2-R^8, where L is a halide (see above Wittig reference for relevant procedures), Horner-Wadsworth-Emmons reagents may be made from the same precursor using an Arbuzov-Michaelis reaction (*Chem. Rev.*, **1984**, *45*, 577) and finally, Peterson reagents made be made from the same precursor following the precedents in the *Org. React.* reference above. Functionalities contained within W^1, W^2, Z^1 or Z^2 that may be incompatible with this chemistry may either be protected as described previously or installed after functionalization at C-4.

Alternatively, these compounds may be made via the following chemistry:

For example, the compound of formula **51** where R^5 is defined as above, X^1 is CR^9R^{10}, X^2 is O and R^8 is H may be prepared through the corresponding α,β-unsaturated ester intermediates derived from Wittig, Horner-Emmons or Peterson olefination of the C5 ketone of **38**. For instance, when CR^9R^{10} is CH_2, (carbethoxymethylene)triphenylphosphorane or (carbethoxyethylidene)triphenylphosphorane can be reacted with ketone **38** in an aprotic solvent, such as toluene or diethyl ether, to provide the unsaturated ethyl ester. This compound may then be reduced, for instance with diisobutyl aluminum hydride in an aprotic solvent, such as toluene or diethyl ether at a temperature ranging from -78°C to 25°C, to produce the desired allyl alcohol.

The compound of formula **51** where R^5 is defined as above, X^1 is a bond, X^2 is a bond and R^8 is $-C(O)OR^3$ or $C(O)NR^9R^3$ wherein R^3 and R^9 are defined above, may be prepared first by hydrolysis of the above unsaturated ethyl ester, for example with sodium hydroxide or lithium hydroxide in a solvent mixture containing water and some organic solvent such as tetrahydrofuran and then by esterification, with $HO-R^3$, or amidation, with HNR^9R^3 using standard coupling reagents such as EDC, DEPC, DCC, CDI or EEDQ in a solvent such as dichloromethane, DMF or chloroform at a temperature ranging from 0°C to 25°C.

The compound of formula **51** where R^5 is defined as above, X^1 is CH_2, X^2 is O and R^8 is $-C(O)R^3$, wherein R^3 is defined above, may be prepared via acylation of allyl alcohol described above; for example by treatment of said alcohol with $L-C(O)R^3$, wherein L is a leaving group such as Cl, Br or N-hydroxysuccinimide (NHS) ester, in the presence of a base, such as sodium hydride, triethylamine or potassium *tert*-butoxide in a solvent such as THF or dioxane at a temperature ranging from 0°C to 65°C.

The compound of formula **51** where R^5 is defined as above, X^1 is CH_2, X^2 is O and R^8 is equal to R^3, may be prepared via alkylation of allyl alcohol described above; for example by treatment of said alcohol with $L-R^3$, wherein L is a leaving group such as Cl, Br or mesylate, in the presence of a base, such as sodium hydride, triethylamine or potassium *tert*-butoxide in a solvent such as THF or dioxane at a temperature ranging from 0°C to 65°C.

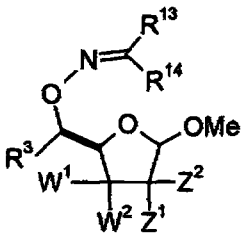
The compound of formula **51** where R^5 is defined as above, X^1 is CH_2, X^2 is O or S, and where R^8 is $-(CH_2)_m(C_6-C_{10}$ aryl), wherein "m" is 0, may also be prepared via a Mitsunobu reaction. The allyl alcohol, prepared as described above, is subjected to Mitsunobu reaction with $HO-(CH_2)_m(C_6-C_{10}$ aryl), or $HS-(CH_2)_m(C_6-C_{10}$ aryl), mediated by triphenylphosphine and diethyl azodicarboxylate as described in *Org. Reactions*, **1992**, *42*, 335. The resulting thioether may be oxidized, for instance with *m*-CPBA to get to the compound where X^2 is SO_2.

The compound of formula **51** where R^5 is defined as above, X^1 is CH_2, X^2 is O and R^8 is $-C(O)NR^9R^3$, may be prepared by reacting allyl alcohol, prepared as described above, with isocyanate $OCNR^3$ in toluene at temperatures from 40°C to 110°C, preferably 50°C to 80°C. Addition of dimethylaminopyridine and triethylamine to the reaction may be advantageous. The R^9 group may be subsequently added via alkylation of carbamate with R^9-L, where L is a leaving group such as Cl, Br or N-hydroxysuccinimide (NHS) ester, in the presence of a base, such as sodium hydride, triethylamine, n-butyl lithium or potassium *tert*-butoxide (see *J. Het. Chem.*, **1988**, *25*, 148 or *Synthesis*, **1985**, 856).

The compound of formula **51** where R^5 is defined as above, X^1 is CH_2, X^2 is NR^9 and R^8 is defined as above, with the proviso that nitrogen is not adjacent to a carbonyl functionality, may be prepared via reduction amination of the aldehyde, prepared by the

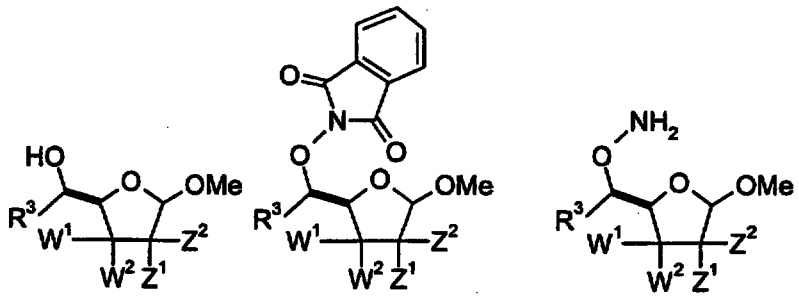
oxidation of the allyl alcohol above: (1) the allyl alcohol may be oxidized, for example using Swern conditions as described in *Org. Reactions*, **1990**, *39*, 297, (2) and combined with HNR^9R^8 in an inert solvent and then (3) treated with a reducing agent such as $NaBH_4$, $NaBH(OAc)_3$, or $NaCNBH_3$. R^9 may be introduced as part of HNR^9R^8 in step (2) or introduced after step (3), wherein H_2NR^8 was used, via alkylation, for instance with a base such as sodium hydride or potassium *tert*-butoxide and an alkylating agent such as R^9-L where is L is Br, Cl or methanesulfonate in a solvent such as THF or dioxane at a temperature ranging from 0°C to 65°C.

The compound of formula **51** where R^5 is defined above, X^1 is CH_2 and where X^2 is NR^9 and X^2 and R^8 are taken together as described above may be prepared by the reaction of HX^2R^8 with the derived allyl mesylate in the presence of an amine base, such as triethylamine or pyridine. The allyl mesylate may be prepared by the reaction of the allyl alcohol described above with methanesulfonyl chloride in the presence of an amine base, such as triethylamine or pyridine.

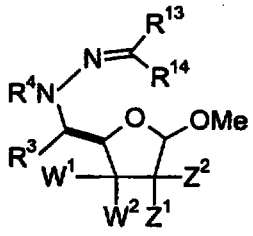


52

Compound **52** can be prepared from compound **49**. Reduction with sodium borohydride provides alcohol **53**. Conversion of **53** to the phthalimide derivative **54** can be carried out through a Mitsunobu reaction (*Synthesis*, **1981**, 1) or via formation of the triflate from **53** through reaction with trifluoromethanesulfonyl chloride and dimethylaminopyridine in an aprotic solvent such as dichloromethane, followed by displacement with N-hydroxyphthalimide at a temperature ranging from 0°C to 25°C. Cleavage of the phthalimide group by treatment with hydrazine or aqueous methylamine yields the corresponding hydroxylamine **55**, which can be transformed to **52** by reaction with an aldehyde or ketone $R^{13}C(O)R^{14}$ in nonprotic solvent such as tetrahydrofuran. If W^1 and W^2 or Z^1 and Z^2 are taken together to form a ketone, it may be necessary to protect it, for instance as a dimethyl ketal through the use of methanol and catalytic acid such as camphorsulfonic acid or p-TsOH. Deprotection of the ketal can be carried out concomitantly with the cleavage of the anomeric methyl acetal to generate the hydroxyl group at C-1. Alternatively, a ketone may be masked as its protected alcohol, which can then be regenerated by deprotection and oxidation, for example under Swern conditions.

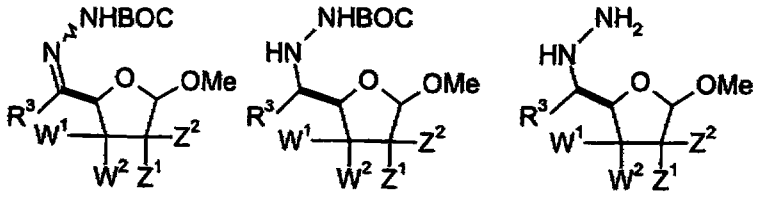


53 54 55

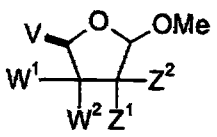


56

Compound **56** is prepared from ketone **49**. Reaction with t-butoxycarbonyl-hydrazine provides compound **57**, which can be hydrogenated to yield compound **58** (*J. Org. Chem.*, **1976**, *41*, 3805). Removal of the BOC group with TFA or dry HCl in absolute ethanol gives the hydrazine **59** (*J. Org. Chem.*, **1976**, *41*, 3805), which can be condensed with aldehyde or ketone $R^{13}C(O)R^{14}$ in an inert solvent such as tetrahydrofuran or methanol to provide compound **56**. When R^4 is not H, N1-substituted t-butoxycarbonyl-hydrazine, which can be prepared by alkylation of t-butoxycarbonyl-hydrazine (*J. Org. Chem.*, **1965**, *30*, 321), can be employed in the reaction with ketone **49**. If W^1 and W^2 or Z^1 and Z^2 are taken together to form a ketone, it may be necessary to protect it, for instance as a dimethyl ketal through the use of methanol and catalytic acid such as camphorsulfonic acid or p-TsOH. Deprotection of the ketal can be carried out concomitantly with the cleavage of the anomeric methyl acetal to generate the hydroxyl group at C-1. Alternatively, a ketone may be masked as its protected alcohol, which can then be regenerated by deprotection and oxidation, for example under Swern conditions.

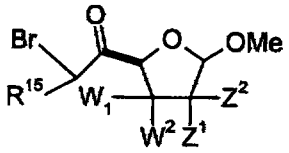


57 58 59



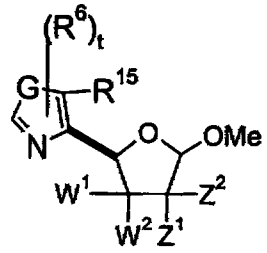
60

Compound **60**, where V is a carbon-linked heterocycle as described for the compound of formula **1**, may be prepared from **61**, which in turn may be prepared from **49**, wherein R^3 is $R^{15}CH_2$- and R^{15} is any of the moieties in the definition of R^3 that may be attached through a methylene group. For example, reaction of **49** with triethylamine and trimethylsilyl triflate in an aprotic solvent, preferably dichloromethane, at temperatures between 0 °C and -40 °C, preferably -15 °C to -30 °C, and then reaction of the resultant silyl enol ether with N-bromosuccinimide and a base such as sodium hydrogen carbonate in a solvent such as THF or dioxane at a temperature ranging from 0°C to 30°C, may lead to α-bromo ketone **61**.



61

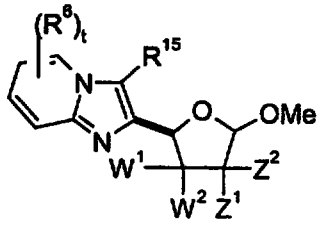
Compound **62**, where G is O, S or N and t is an integer between 0-3, may be prepared by reaction of **61** with a thioamide, amide or amidine following the precedent of *J. Het. Chem.*, **1991**, *28*, 907, *J. Org. Chem.*, **1990**, *55*, 1479 and *Synth. Commun.*, **1979**, 9, respectively. Thioamide, amide or amidine starting materials are generally commercially available.



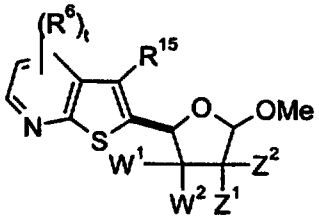
62

To prepare fused heterocycles a variety of chemistries may be utilized depended on the desired product. For example, one may react **61** with a 2-aminopyridine to produce **63**

based on the precedent in *J. Het. Chem.*, **1989**, *26*, 293. One may react **61** with a thioxodihydropyridine to produce **64** based on the precedent in *Tetrahedron*, **1978**, 34. One may react **61** with an aminophenol to produce **65** based on the precedent in *Synth. Comm.*, **1987**, *17*, 341. One may react **61** with an aniline to produce **66** or a phenylenediamine to produce **67** based on the precedents in *Aust. J. Chem.*, **1980**, 33 and *J. Chem. Soc.*, **1953**, *485*, 487, respectively. One may react **61** with a benzaldehyde to produce **68** based on the precedent in *Synthesis*, **1990**, 253.



63



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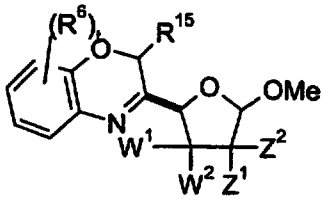

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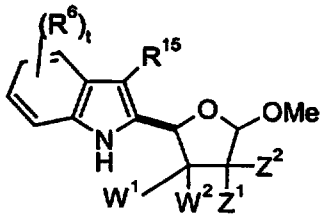
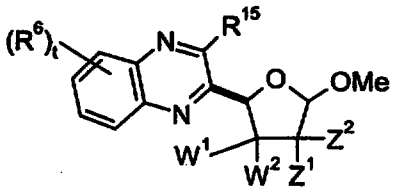
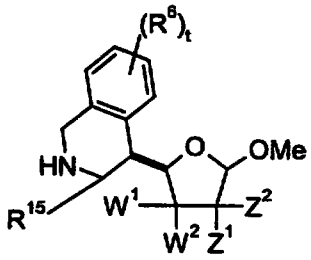


66

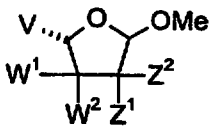


67

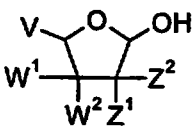


68

Similar modifications to those described above can be carried out on **28**, the C-4 isomer of **16**, to provide **69**, with opposite stereochemistry at C-4. V, W^1, W^2, Z^1 and Z^2 of compound **69** are as described for the compound of formula **1**.



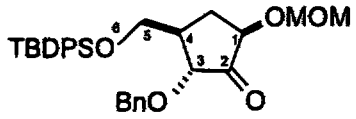
69



Fragment C

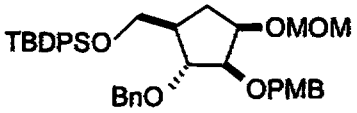
Fragment C is prepared by removal of the C-1 methyl acetal from compounds **29** or **69**. This can be carried out via treatment with aqueous trifluoroacetic acid, and provides a hydroxy group at C-1 for attachment to fragment B.

Compounds wherein Y is CH_2 can be made using the chemistry below.



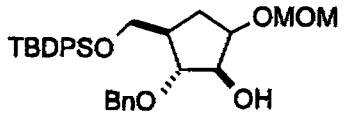
70

Compound **70** may be prepared from available starting material **71** (*Bull. Chem. Soc. Jpn.*, **1987**, *60*, 3673).

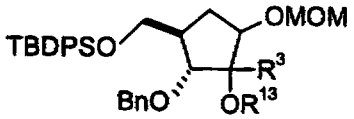


71

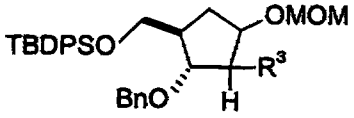
For instance, selective removal of the p-methoxybenzyl ether can be carried out with ceric ammonium nitrate or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in a mixture of organic and aqueous solvents at a temperature ranging from 0°C to 65°C, preferably from 0°C to 25°C. The resulting alcohol, **72**, may be oxidized, for example under Swern (*J. Org. Chem.*, **1976**, *41*, 3329) or Dess-Martin (*J. Org. Chem.*, **1983**, *48*, 4155) conditions, to lead to compound **70**.



72

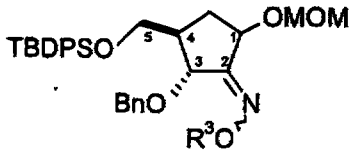


73



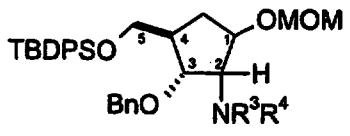
74

Compounds **73** and **74** may be prepared from either **72** or **70** using the methods described for the preparation of **7** and **8**.



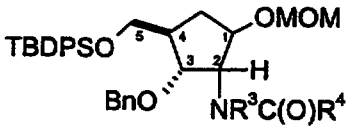
75

Compound **75**, where Z^1 and Z^2 are taken together to form an oxime of the formula $=NOR^3$, wherein R^3 is as defined above, may be prepared by the methods described for the preparation of **9**.



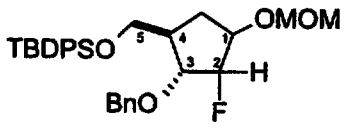
76

Compound **76**, wherein R^3 and R^4 are as defined above, may be synthesized by reductive amination at the C-2 ketone site of the compound of formula **70** using the methods described for the preparation of **10**. Both C-2 diastereomers are available using this chemistry.



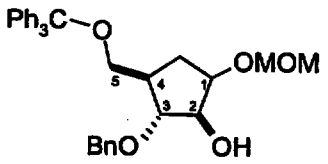
77

Compounds of the formula **77** can be prepared by the methods described for the preparation of **11**.



78

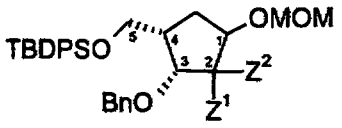
Compound **78**, may be prepared from available starting material **79** which in turn can be prepared from **72**.



79

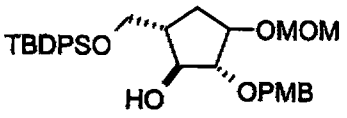
For instance, the TBDPS group can be removed using tetrabutylammonium fluoride (TBAF) in a solvent such as THF at a temperature ranging from 0°C to 65°C, preferably from 0°C to 25°C. The resultant alcohol can be converted to **79** by treatment with triphenylmethyl chloride and a base such as triethylamine in an organic solvent such as dichloromethane, dichloroethane, DMF or chloroform at a temperature ranging from 0°C to 65°C, preferably from 0°C to 25°C. Treatment of **79** with diethylaminosulfur trifluoride (DAST) (*Tetrahedron Lett.*, **1991**, *32*, 5963) provides the C-2-F intermediate. Removal of the trityl group using mild acid, for example p-toluenesulfonic acid in MeOH (*Tetrahedron Lett.*, **1981**, *22*, 1299), followed by silylation of the resultant primary alcohol with TBDPS-Cl, for example in

dichloromethane or DMF in the presence of an amine base, may be used to complete the preparation of **78**. The other C-2 diastereomer may be obtained by first inverting the C-2-OH of **79** by Mitsunobu inversion as described previously for compound **6**.

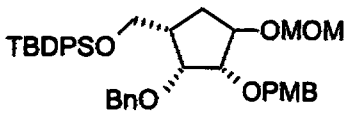


80

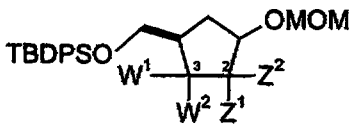
Compound **80** may be prepared from available starting material **81** which can prepared from L-glucose using chemistry described in the preparation of **71** (*Bull. Chem. Soc. Jpn.*, **1987**, *60*, 3673). Compound **82** can be obtained by Mitsunobu inversion of the C-3-OH followed by treatment of the alcohol with benzyl bromide and a suitable strong base such as sodium hydride or potassium carbonate in a polar aprotic solvent, such as tetrahydrofuran or dimethylformamide at a temperature ranging from 0°C to 65°C, preferably from 0°C to 25°C.



81

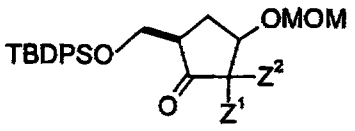


82



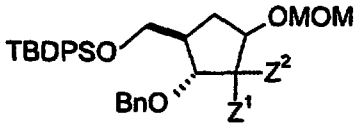
83

Functionalization of the C-3 position can be carried out on the substrates described above, such that the desired moieties are installed at both the C-2 and C-3 positions to generate intermediate **83**, where W^1, W^2, Z^1 and Z^2 are as described in formula **1**, or are present as their precursors, protected precursors, or protected derivatives.



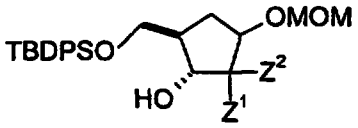
84

Compounds **84** may be prepared from compound **85**, which represents compounds **70**, **73**, **74**, **75**, **76**, **77**, and **78** described above.

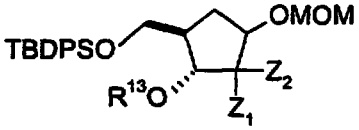


85

Removal of the benzyl group from **85** can be carried out by hydrogenation, for instance with hydrogen gas and a catalyst such as palladium on carbon, or by use of a hydrogen transfer agent such as cyclohexadiene and palladium on carbon in a solvent such as THF or methanol at a temperature ranging from 0°C to 25°C, to provide alcohol **86**. Oxidation of **86** by the methods cited for **72** above generates **84**.

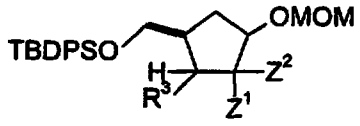


86



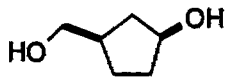
87

Compounds **87** can be prepared from **84** and **86** using the chemistry described for synthesis of **73**.

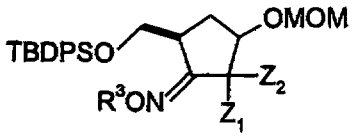


88

Compounds **88** can be prepared from **84** using the chemistry described for synthesis of **74**. Compounds **88** wherein R^3 is H can be obtained by the removal of the 3-OH of compound **86** by Barton-McCombie deoxygenation (*J. Chem. Soc. Perkin I*, **1975**, 1574). Compound **83** where W^1, W^2, Z^1 and Z^2 are each H, can be accessed by elaboration of **89** (*Chem. Ber.*, **1988**, *121*, 485), through tert-butyldiphenylsilyl ether formation on the primary alcohol, followed by introduction of a MOM group on the C-1 hydroxyl group.

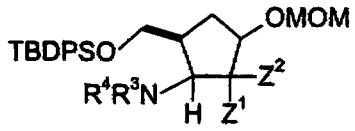


89



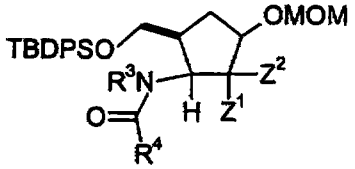
90

Compounds **90** can be synthesized from **84** as described for preparation of compound **75**.



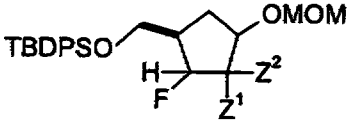
91

Compounds **91** can be prepared from compound **84** as described for **76**.



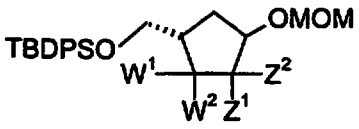
92

Compounds **92** can be prepared from **84** or **86** using the chemistry described for **77**.



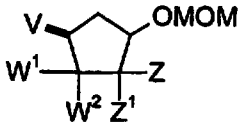
93

Compounds **93** can be prepared from **85** through removal of the TBDPS ether, for instance with a fluoride source such as TBAF in a solvent such as THF at a temperature ranging from 0°C to 25°C, and installation of a trityl protecting group on the primary alcohol through use of, for instance, trityl chloride and pyridine in a solvent such as dichloromethane at a temperature ranging from 0°C to 25°C. Debenzylation as described for **85** is then followed by the elaboration described for preparation of compound **78** above.



94

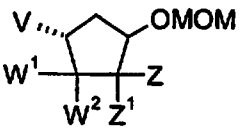
Compound **94**, wherein the substituent at the C-4 position is in the α-orientation, can be prepared from **80**, using the chemistry described above for its isomer **85**.



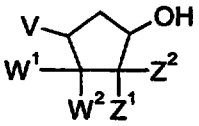
95

At this stage, the tert-butyldiphenylsilyloxymethyl substituent at the C-4 position of intermediates **83** can be modified to provide key intermediates for introduction of V, as defined in the compound of formula **1**. These compounds are then used to prepare compound **95**, wherein V is as described in the compound of formula **1**. These compounds are prepared from **83** using the chemistry described for compounds **29 - 68**.

Similar modifications to those described above can be carried out on **94**, the C-4 isomer of **83**, to provide **96**, with opposite stereochemistry at C-4. V, W^1, W^2, Z^1 and Z^2 of compound **96** are as described for the compound of formula **1**.



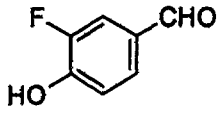
96



Fragment C

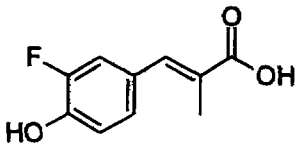
Fragment C is prepared by removal of the C-1 methoxymethyl ether from compounds **95** or **96**. This can be carried out via treatment with aqueous trifluoroacetic acid, and provides a hydroxy group at C-1 for attachment to fragment B.

Preparation of Fragment B and Coupling to Fragments A and C



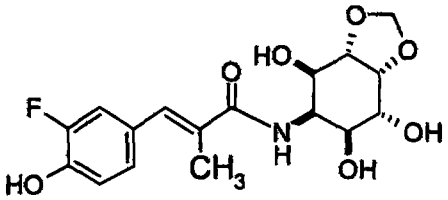
97

Compound **97** can be prepared by treatment of 3-fluoro-4-methoxybenzaldeyde with BBr_3, BI_3 or TMSI, preferably BBr_3, in a solvent such as dichloromethane at a temperature ranging from 0°C to 65°C, preferably from 0°C to 25°C.



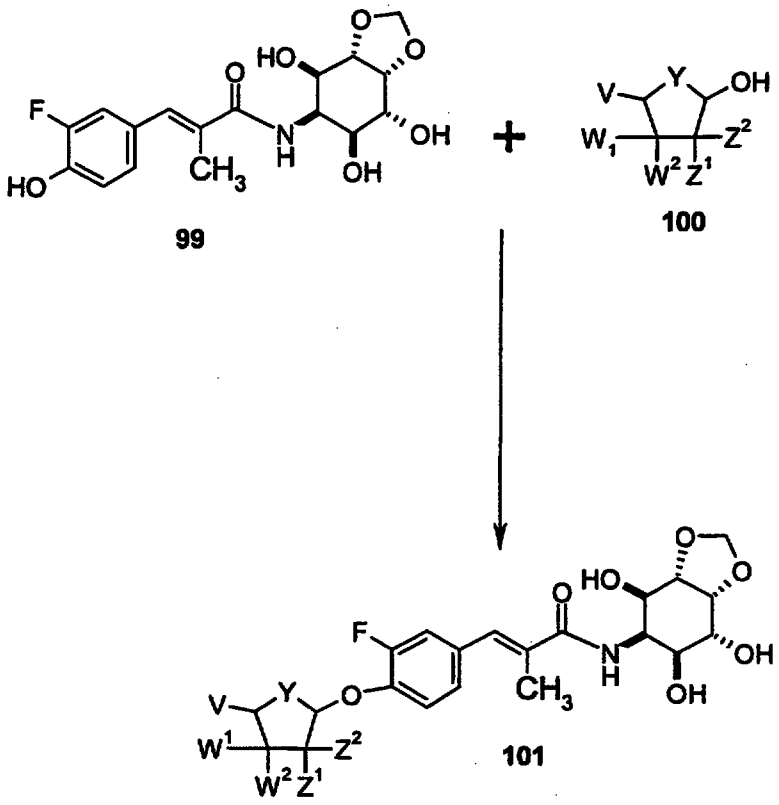
98

Compound **98** can be prepared by treatment of **97** with $Ph_3P=C(CH_3)CO_2Et$ in a solvent such as dichloromethane. The resultant ester can then be hydrolyzed with hydroxide as its lithium, sodium or potassium salt, preferably a 5-10 fold excess of the lithium salt in a mixture of organic solvents such as methanol, THF, Et_2O, dioxane and water preferably in a mixture of 3THF:2methanol:1water at a temperature ranging from 0°C to 65°C, preferably from 0°C to 25°C.



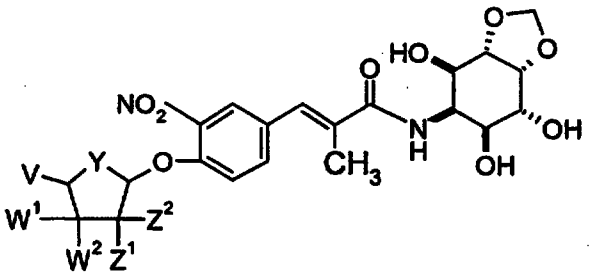
99

Compound **99** can be prepared by treatment of a solution of compounds of the formula **2** and **98** with an appropriate acid coupling reagent such as DCC, EDCI, BOPCl, PYBROP or 2-ethoxy-1-ethoxylcarbonyl-1,2-dihydroxyquinoline (EEDQ) in a polar aprotic solvent such as DMSO or DMF, preferably DMF, at a temperature ranging from 0°C to 65°C preferably from 25°C to 65°C.



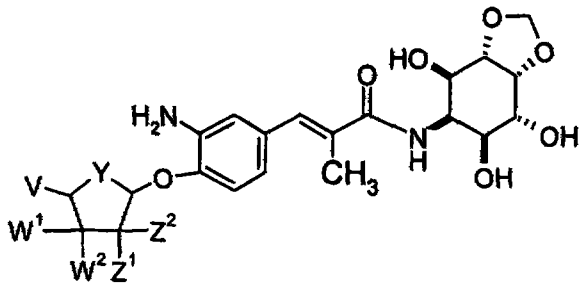
99 100 101

Compounds of the formula **101** can be prepared by treatment of compound **100** with dialkylazodicarboxylate, wherein alkyl is preferably ethyl, propyl, isopropyl, or tert-butyl; and triphenylphosphine or triphenylphosphine attached to a suitable polymer support; in a suitable organic solvent such as THF, Et_20, dioxane at a temperature ranging from 0°C to 65°C, preferably from 0°C to 25°C



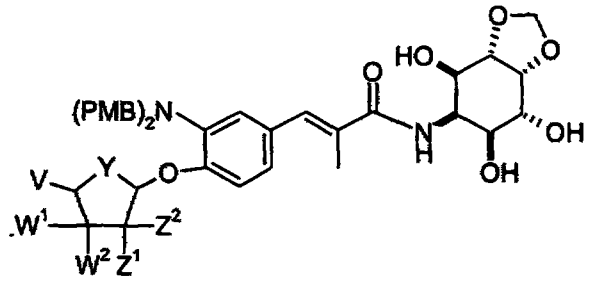
102

Compound **102** can be prepared from 4-hydroxy-3-nitrobenzaldehyde using the scheme outlined for the synthesis of compound **101**.

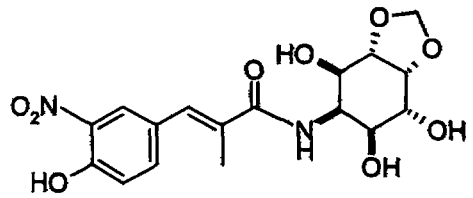


103

The compound of the formula **103** can be prepared by selective reduction of the aromatic nitro group using hydrogenation over Pd/C (*Chem. Pharm. Bull.*, **1997**, *45*, 1984). Alternatively compound of the formula **103** can be prepared from **104** by treatment with trifluoroacetic acid.

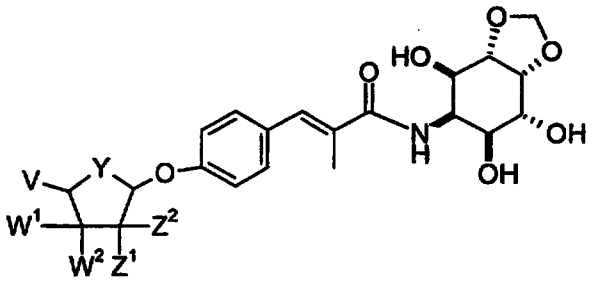


104



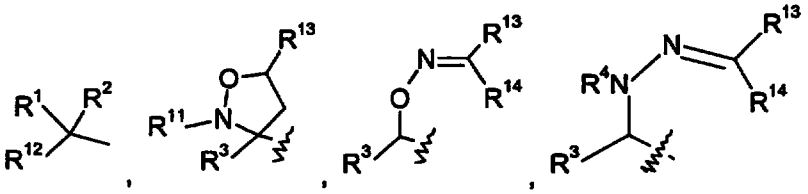
105

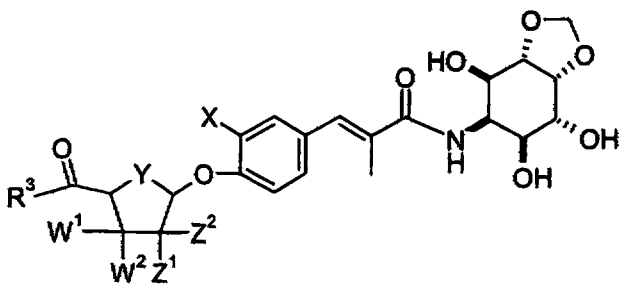
Compound of the formula **104** can be obtained from compound **105** which was prepared using the scheme outlined for **101**. Reduction of the nitro group using Pd/C as above is followed by protection of the amine as its bis-4-methoxybenzyl ether. Coupling with **100** as described above can provide **104**.



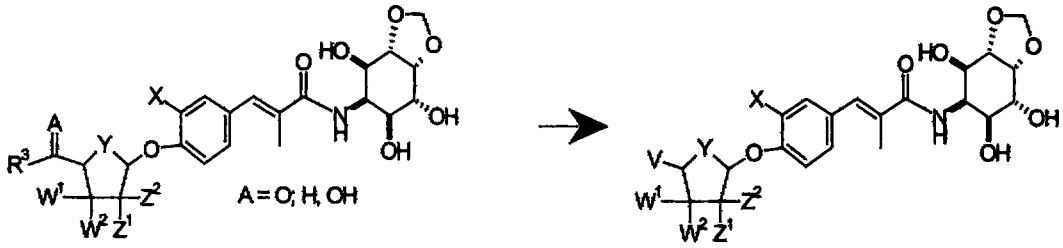
106

The compound of the formula **106** can be prepared from 4-hydroxybenzaldehyde using the scheme outlined for the synthesis of compound **101**.

Alternatively, through coupling of fragments B and A to Fragment C wherein Y, W^1, W^2, Z^1 and Z^2 are as defined in the compound of formula **1** and V equals $R^3C(O)$, as in compound **49**, compound **107** may be prepared. Reduction of the 5"-ketone or aldehyde to the alcohol at that position may be carried out through the action of sodium borohydride in methanol. Modification of **108**, the ketone or aldehyde or their derived alcohols, can then be carried out as described above for **37**, **38** and **49** to prepare compounds of the formula **1** wherein V =  or a carbon-linked heterocyclic group as defined for formula **1**.

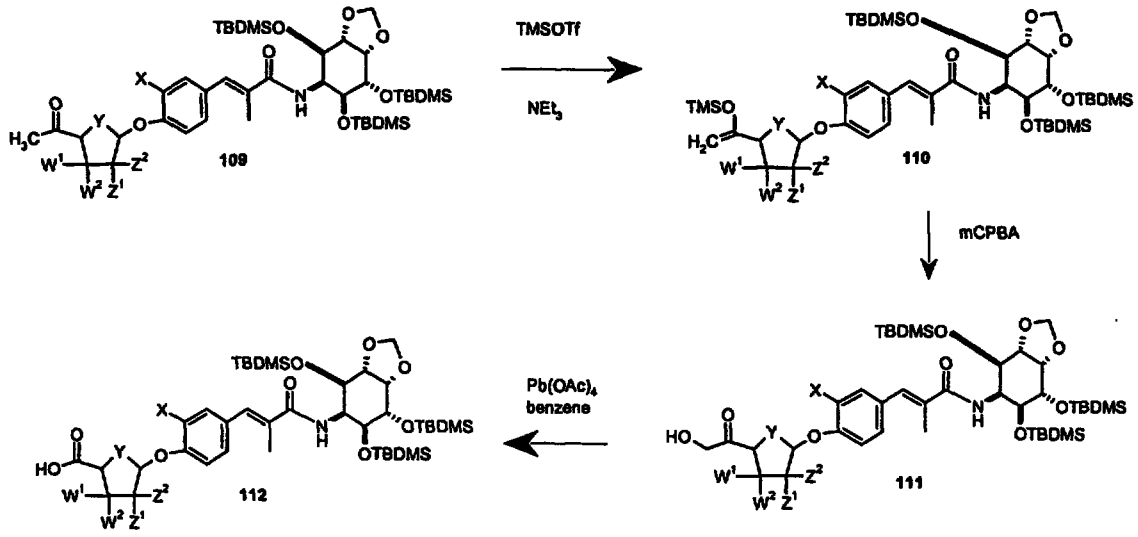


107



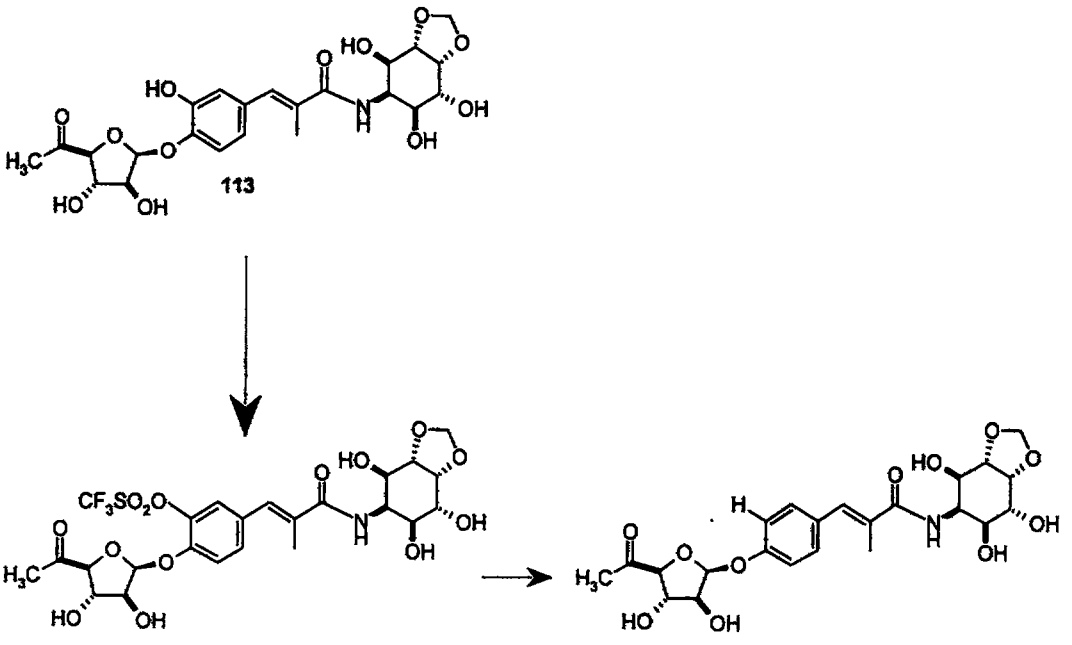
108 1

Compound **107** (preferentially where R^3 = Me) may also be transformed into compounds of the formula **1** wherein V = $R^3OC(O)$, $R^3R^4NC(O)$ or $(R^3O)R^4NC(O)$. Protection of labile functional groups in **107** is effected first. For instance, hydroxyl groups may be protected as their TBDMS ethers, for instance through treatment with >10 equivalents tert-butyldimethylsilyl chloride (TBDMSCl) and >10 equivalents of imidazole in DMF at a temperature of 60°C to 90°C. The ketone **109** is then converted to its trimethylsilyl enol ether **110** via treatment with TMS triflate and triethylamine, followed by reaction with meta-chloroperoxybenzoic acid and acidic workup, which provides α-hydroxy ketone **111**, as described for conversion of **38** to **46**. Lead tetraacetate ($Pb(OAc)_4$) in benzene, at a temperature of 10°C to 40°C then converts compound **111** to carboxylic acid **112**. Using the chemistry described for transformation of **32** to **33**, **34** and **35**, followed by deprotection if necessary, **112** can be converted to compounds of the formula **1** wherein V = $R^3OC(O)$, $R^3R^4NC(O)$ or $(R^3O)R^4NC(O)$. Remaining TBDMS protecting groups can be removed by treatment with a fluoride source such as tetrabutyl ammonium fluoride in tetrahydrofuran or HF in pyridine and tetrahydrofuran at temperatures ranging from 10°C to 40°C.

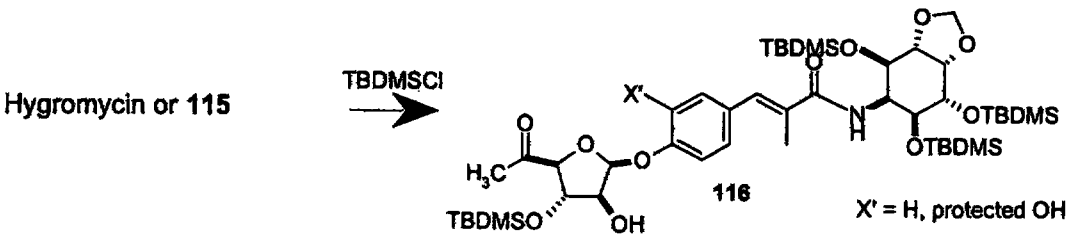


Preparation from Hygromycin A

Alternatively, some of the compounds of formula **1** can be prepared from the natural product hygromycin. For example, the phenolic hydroxyl group of hygromycin can be removed to generate an analogue of the natural product wherein the substituent identified as X in the compound of formula **1** is H in the following manner. Compound **114** can be prepared by treatment of the corresponding compound **113** (hygromycin A) with trifluoromethanesulfonyl anhydride or N-diphenyltrifluoromethanesulfonyl amide in the presence of an amine base such as triethylamine in a solvent such as DMF or a mixture of DMF and dichloromethane at a temperature ranging from 0°C to 65°C, preferably from 0°C to 25°C. Treatment of compound **114** with $Pd(PPh_3)_4$ in DMF at a temperature ranging from 0°C to 65°C, preferably from 0°C to 25°C can provide compound of the formula **115** (ref).

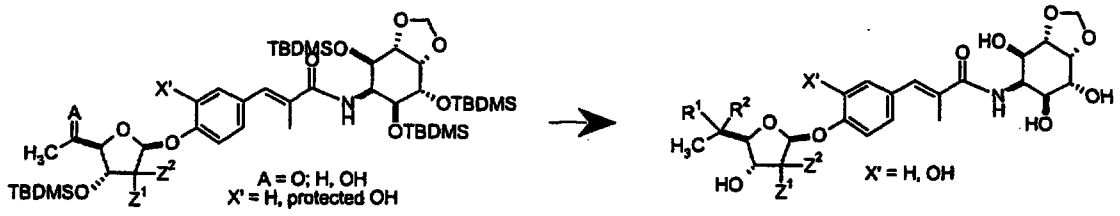


Selective protection can be carried out on hygromycin A and **115** through reaction with 10 equivalents of tert-butyldimethylsilyl chloride and imidazole in DMF at a temperature of 25-40°C, to provide compound **116**. It may be necessary to reprotect the phenolic hydroxyl group in the course of elaboration of the 2" position due to the lability of the TBDMS ether at this position. An allyl group, for instance, can be introduced through reaction with allyl bromide and potassium carbonate. Removal of the allyl group may be carried out at a later stage, for instance through use of iridium-mediated isomerization and subsequent hydrolysis (*J. Antibiotics*, **1992**, *45*, 1705) or through the use of palladium chemistry (*Tetrahedron Lett.*, **1994**, *35*, 4349 and *Synthesis*, **1996**, 755).

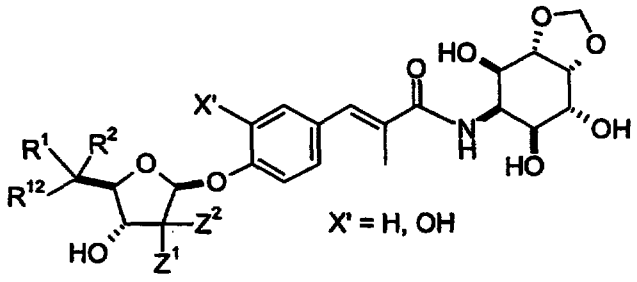


Compound **118** may be prepared from compound **116**. Use of the chemistry described in the elaboration of the Z^1 and Z^2 groups starting from compound **6** provides intermediate **117**, where A = O. It may be necessary to protect the 5"-ketone of **116**, for example as its 1,3-dioxolane (using the procedure in *J. Org. Chem.*, **1991**, *56*, 2976), during the elaboration of the Z^1 and Z^2 functionality. The acetal may subsequently be cleaved back to the ketone through use of TFA and water (*J. Org. Chem.*, **1991**, *56*, 2976); it may be

necessary to re-introduce the TBDMS groups at this point, if protection of the hydroxy functions is required for subsequent chemistry. Use of other protecting groups, such as acetyl, allyl, benzyl, and p-methoxybenzyl, may be advantageous, depending on the chemistry carried out at 2", 5" and elsewhere in the molecule, in this and subsequent preparations. Reduction of the 5"-ketone to the alcohol at that position may be carried out through the action of sodium borohydride in methanol. Modification of **117**, the ketone or its derived alcohol, can then be carried out as described above for **37** and **38**. Removal of the TBDMS protecting groups can be carried out by treatment with HF in pyridine, to generate **118**.

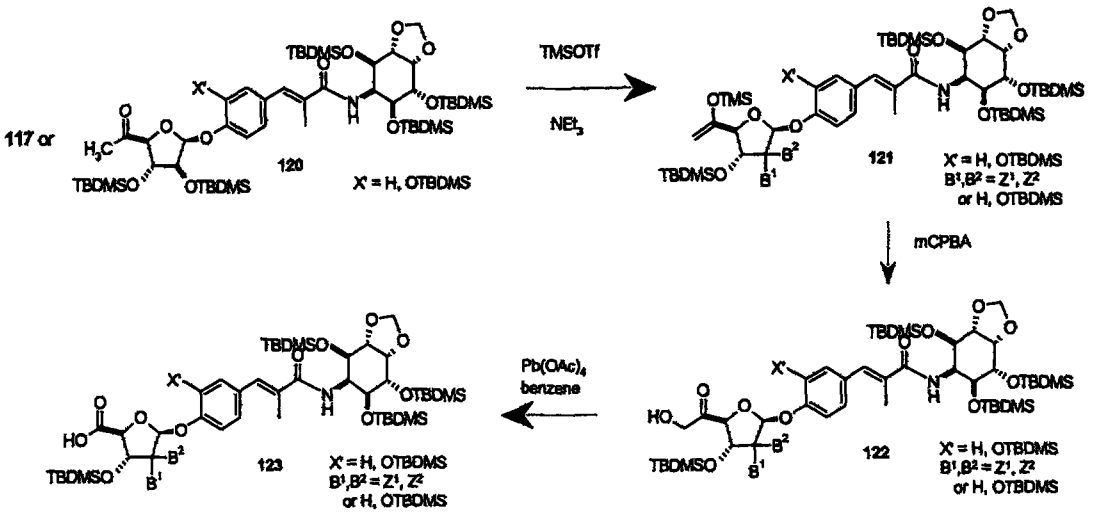


117 **118**

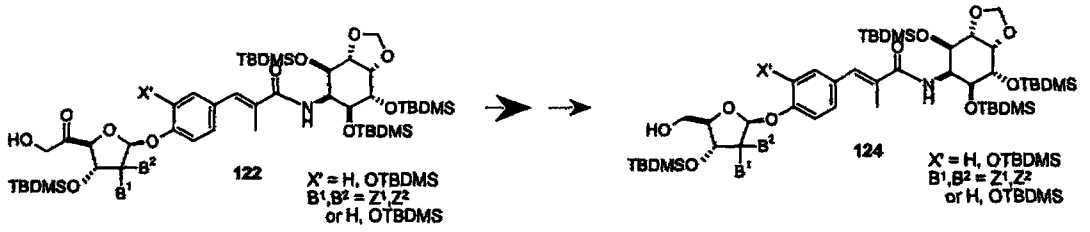


119

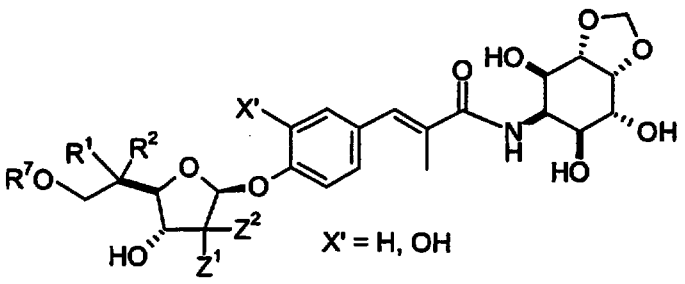
Compounds **119** may be prepared from persilylated derivatives **117** or **120**, which is prepared from hygromycin or compound **115** through treatment with 12 equivalents tert-butyldimethylsilyl chloride and 12 equivalents of imidazole in DMF at a temperature of 60-90°C, preferably 75-85°C. Formation of trimethylsilyl enol ether **121** via treatment with TMS triflate and triethylamine is followed by reaction with meta-chloroperoxybenzoic acid. Acidic workup leads to α-hydroxy ketone **122**. Lead tetraacetate in benzene converts compound **122** to carboxylic acid **123**, in a sequence analogous to that described for conversion of **109** to **112**.



Similar treatment of **122** with lead tetraacetate in methanol provides the methyl ester at 5", which can be reduced with lithium borohydride to provide alcohol **124**.

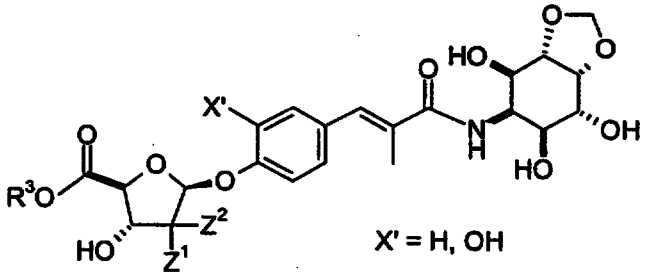


Modification of **123** and **124** as described above for **32** and **30** serves to install R^1, R^2 and R^{12}, as described for the compound of formula **1**. It may be necessary to reprotect the phenolic hydroxyl group in the course of this elaboration due to the lability of the TBDMS ether at this position. An allyl group, for instance, can be introduced through reaction with allyl bromide and potassium carbonate. Removal of the allyl group may be carried out at a later stage, for instance through use of iridium-mediated isomerization and subsequent hydrolysis (*J. Antibiotics*, **1992**, *45*, 1705) or through the use of palladium chemistry (*Tetrahedron Lett.*, **1994**, *35*, 4349 and *Synthesis*, **1996**, 755). Final deprotection of the TBDMS groups can then be carried out by treatment with fluoride ion, for instance reaction with hydrogen fluoride in pyridine, to generate compounds **119**.



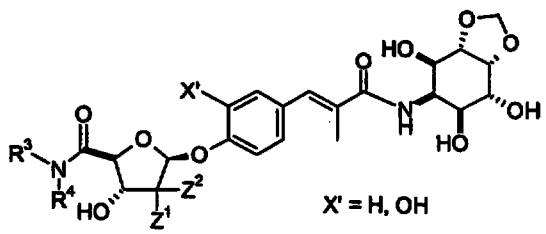
125

Compounds **125**, where R^{12} can be written as $R^7O(CH_2)$-, may be prepared using compounds **122**, through use of the chemistry described for conversion of **46** to **47**. It may be necessary to protect the phenolic hydroxy group, as for instance an allyl ether, during the base-mediated transformations. Further manipulation, as described above for **117**, generates compound **125**.

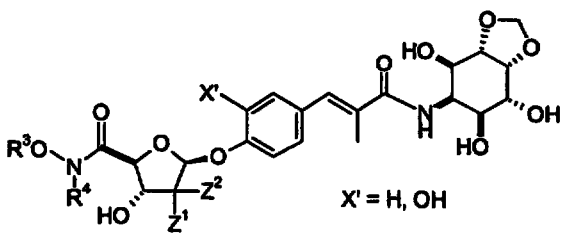


126

Compound **126** may be prepared from **123** by condensation with R^3OH as described for **33**, followed by deprotection.

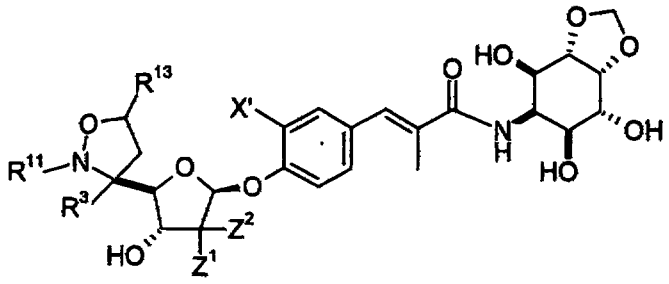


127



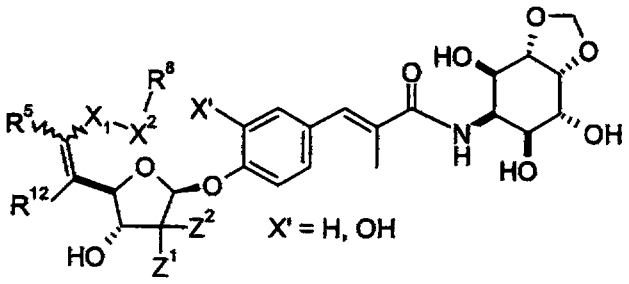
128

Compounds **127** and **128** may be prepared in similar fashion from **123**, by further elaboration to the amide or hydroxamate as described for **34** and **35**, followed by deprotection.



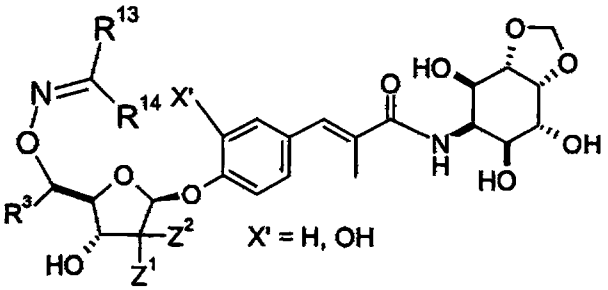
129

Compound **129** may be prepared from compound **119** where R^1 and R^2 are taken together as =O and R^3 was utilized rather than R^{12} in its preparation. Application of the chemistry described for conversion of **49** to **48**, followed by appropriate deprotection, provides **129**.



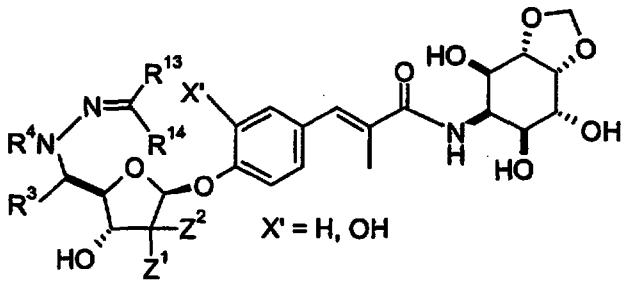
130

Compound **130** may be prepared from compound **119**, where R^1 and R^2 are taken together as =O, using the chemistry described for the preparation of compound **51**.



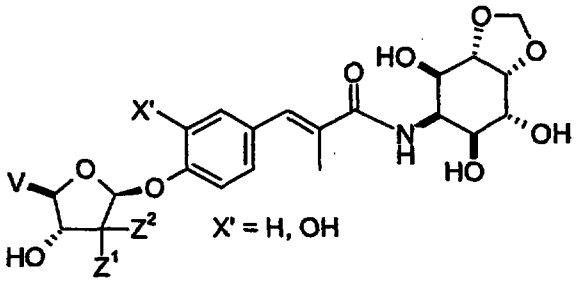
131

Compound **131** may be prepared from ketone **119**, where R^1 is H and R^2 is OH, by the method described for preparation of **52**.



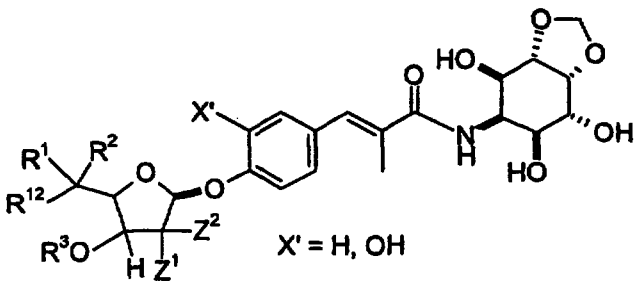
132

Compound **132** may be prepared from ketone **119**, where R^1 and R^2 are taken together as =O, by the method described for preparation of **56**.



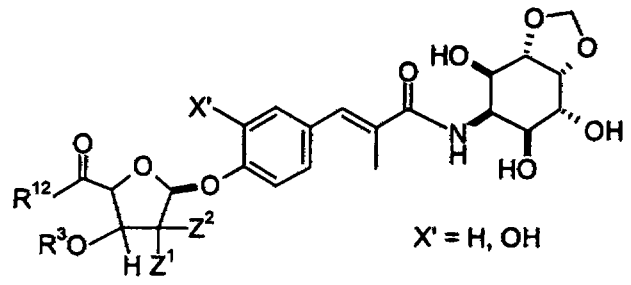
133

Compound **133**, where V is a carbon-linked heterocycle, as described for the compound of formula **1**, may be prepared from ketone **119**, where R^1 and R^2 are taken together as =O, R^{12} is $R^{15}CH_2$- and R^{15} is any of the moieties in the definition of R^{12} that may be attached through a methylene group. Synthesis of **133** is carried out by the method described for preparation of compound **60**, where V is a carbon-linked heterocycle, as described for the compound of formula **1**.

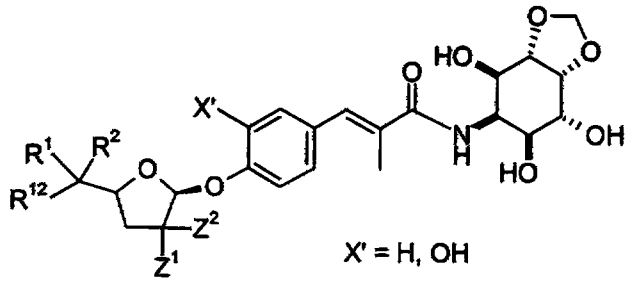


134

Compound **134** may be prepared from **117**, where A is O. Treatment with potassium carbonate and R^3OH at a temperature of 10°C to 40°C provides **135**; an allyl protecting group may be introduced on the phenolic OH of **135** wherein X' = OH, if needed for further chemistry. Compound **134** may then be prepared using the chemistry described for elaboration of compound **117**.

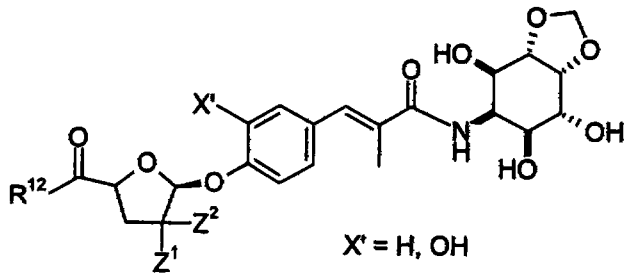


135



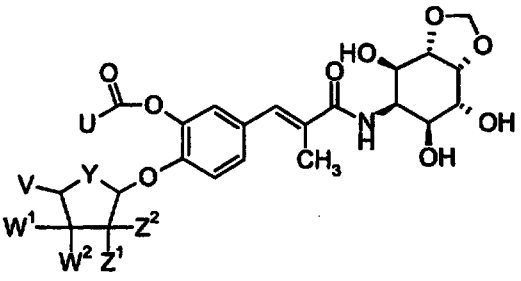
136

Compounds of the formula **136** may be prepared from **119**, where R^1 and R^2 are taken together as =O, through conversion to **137** by the method of Jaynes (*Bioorg. Med. Chem. Lett.*, **1993**, *3*, 1531). Conversion of the hydroxyl groups of **137** to their allyl, silyl, benzyl or p-methoxybenzyl ethers can be followed by conversion of **137** to **136** by the chemistry described for elaboration of **117**.



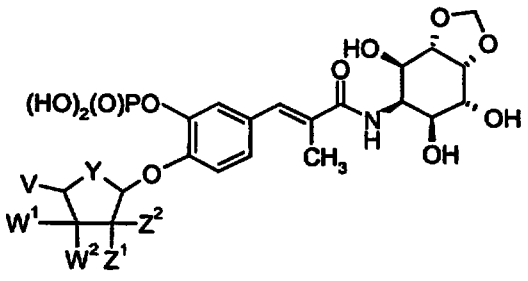
137

Representative prodrugs of the compounds of formula **1** may be prepared using the following chemistry:



138

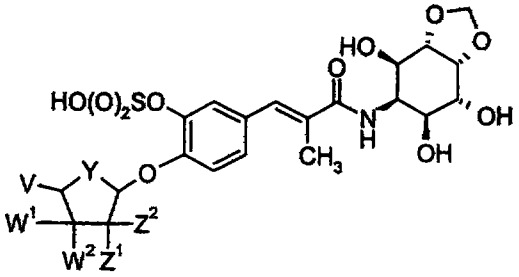
The compound of formula 1 in which X=OH is converted to the corresponding compound of formula **138**, where UC(O)O- comprises an ester prodrug as described in the description of the invention, by reacting 1, in the presence of a base, such as sodium hydride or potassium hydride, with (a) an anhydride compound of the formula, $(UC(O))_2O$, or (b) an acylating agent of the formula, UC(O)L, wherein L is a leaving group such as a halide. If UC(O)- is an amino acid or polypeptide derivative, the amino group can be protected with a CBZ group or t-BOC group (see *Protective Groups in Organic Synthesis*, T. Greene and P. Wuts, Ed., John Wiley & Sons Ltd., New York, 1991). The reaction is stirred in an aprotic solvent, such as tetrahydrofuran, at a temperature range between about -20°C to about 50°C, preferably between -20°C and 10°C. If V, W^1, W^2, Z^1 or Z^2 contains a reactive group toward the reagents used in this transformation, it is necessary to protect such a group prior to this transformation and deprotect at the appropriate time. For example, a primary or secondary amino group might be protected as its 9-fluorenylmethoxy, benzyloxycarbonyl or tert-butoxycarbonyl carbamate. A carboxylic acid can be protected as an ester (see *Protective Groups in Organic Synthesis*, T. Greene and P. Wuts, Ed., John Wiley & Sons Ltd., New York, 1991 or *Protecting Groups*, P. Kocienski, Ed., Thieme Medical Publishers, New York, 1994).



139

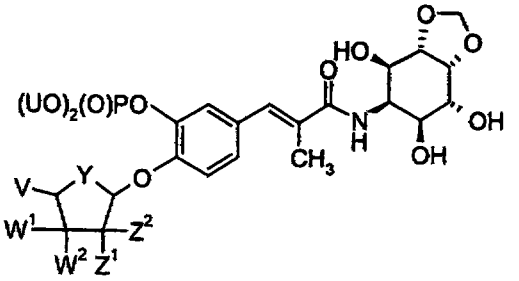
The compound of formula 1 in which X is OH is converted to the corresponding compound of formula **139** by reacting 1, in the presence of a base, such as sodium hydride or potassium hydride, with (a) a compound of the formula, $((PhCH_2O)_2PO)_2O$, or (b) a phosphorylating agent of the formula, $(PhCH_2O)_2P(O)L$, wherein L is chloro or bromo. The

reaction is stirred in an aprotic solvent, such as tetrahydrofuran, at a temperature range between about -20°C to about 50°C, preferably about -20°C and 10°C. The resulting product is then treated with excess cyclohexadiene and Pd/C in ethanol at room temperature to provide a compound of structure **139**. Its alkaline metal salts or alkaline earth metal salts can be prepared by treating **139** in an aqueous solution with, for example, NaOH or $Ca(OH)_2$. If V, W^1, W^2, Z^1 or Z^2 contains a reactive group toward the reagents used in this transformation, it is necessary to protect such a group prior to this transformation and deprotect at the appropriate time, as described for the preparation of compound **138**.



140

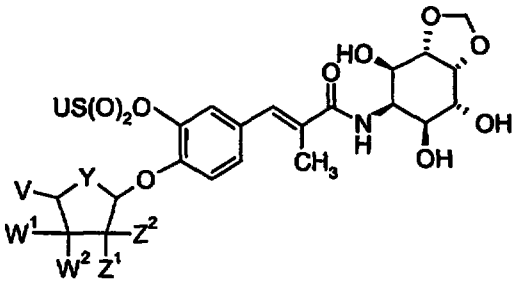
The compound of formula **1** in which X=OH is converted to the corresponding compound of formula **140** by reacting **1**, in the presence of a base, such as sodium hydride or potassium hydride, with sulfur trioxide-DMF complex or sulfer trioxide-pyridine complex (*J. Chem. Soc., Perkin Trans.* 1. **1990**, 1739). The reaction is stirred in an aprotic solvent, such as tetrahydrofuran, at a temperature range between about -20°C to about 50°C, preferably between -15°C to 15°C. Its alkaline metal salts or alkaline earth metal salts can be prepared by treating **140** in an aqueous solution with, for example, NaOH or $Ca(OH)_2$. If V, W^1, W^2, Z^1 or Z^2 contains a reactive group toward the reagents used in this transformation, it is necessary to protect such a group prior to this transformation and deprotect at the appropriate time, as described for the preparation of compound **138**.



141

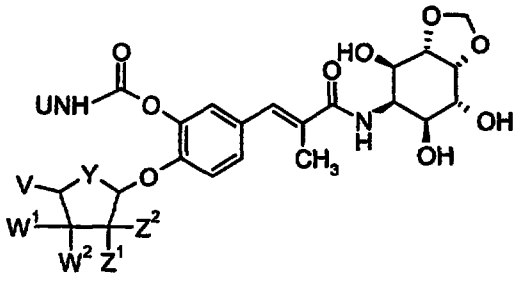
The compound of formula **1** in which X is OH is converted to the corresponding compound of formula **141**, wherein $(UO)_2P(O)O$- comprises a phosphate prodrug as described in the description of the invention, by reacting **1**, in the presence of a base, such as

sodium hydride or potassium hydride, with (a) a compound of the formula, $((UO)_2PO)_2O$, or (b) a phosphorylating agent of the formula, $(UO)_2P(O)_2L$, wherein L is chloro or bromo. The reaction is stirred in an aprotic solvent, such as tetrahydrofuran, at a temperature range between about -20°C to about 50°C, preferably between -10°C to 20°C. If V, W^1, W^2, Z^1 or Z^2 contains a reactive group toward the reagents used in this transformation, it is necessary to protect such a group prior to this transformation and deprotect at the appropriate time.



142

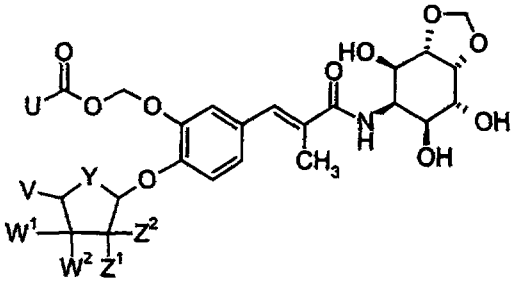
The compound of formula 1 is converted to the corresponding compound of formula **142**, wherein $US(O)_2O$- is a sulfonate prodrug as described in the detailed description of the invention, by reacting 1, in the presence of a base, such as sodium hydride or potassium hydride, with a compound of the formula, $(US(O)_2)_2O$, or (b) $US(O)_2L$, wherein L is chloro or bromo. The reaction is stirred in an aprotic solvent, such as tetrahydrofuran, at a temperature range between about -20°C to about 50°C, preferably between -10°C to 20°C. If V, W^1, W^2, Z^1 or Z^2 contains a reactive group toward the reagents used in this transformation, it is necessary to protect such a group prior to this transformation and deprotect at the appropriate time.



143

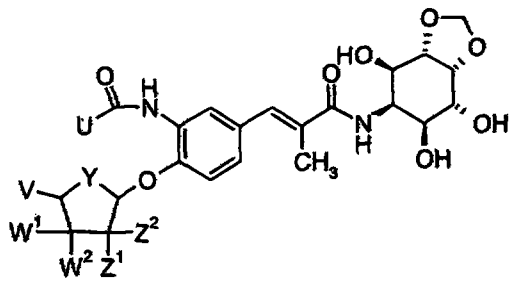
The compound of formula 1 where X is OH is converted to the corresponding compound of formula **143**, wherein UNHC(O)O- is a carbamate prodrug as described in the detailed description of the invention, by reacting 1, in the presence of a base, such as sodium hydride or potassium hydride, with a compound of the formula, UN=C=O. The reaction is stirred in an aprotic solvent, such as tetrahydrofuran, at a temperature range between about -

20°C to about 50°C, preferably between 0°C to 30°C. If U is H, a reagent of the formula $ClSO_2N=C=O$ can be used, followed by treatment with water. If V, W^1, W^2, Z^1 or Z^2 contains a reactive group toward the reagents used in this transformation, it is necessary to protect such a group prior to this transformation and deprotect at the appropriate time.



144

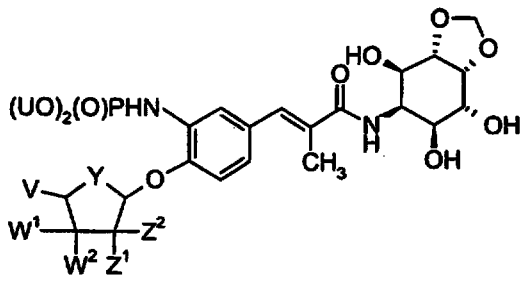
The compound of formula 1 in which X=OH is converted to the corresponding compound of formula **144**, wherein $UC(O)OCH_2O$- is an (acyloxy)methyl ether as described in the detailed description of the invention, by reacting **1**, in the presence of a base, such as sodium hydride or potassium hydride, with an acylating agent of the formula, $UC(O)\text{-}OCH_2O\text{-}L$ (*J. Med. Chem.*, **1996**, *39*, 10). U may also be an N-protected amino acid residue or a polypeptide chain of two or more (e.g., two, three, or four) amino acid residues. For protection of the amino group a CBZ group or t-BOC group can be utilized (see *Protective Groups in Organic Synthesis*, T. Greene and P. Wuts, Ed., John Wiley & Sons Ltd., New York, 1991). The reaction is stirred in an aprotic solvent, such as tetrahydrofuran, at a temperature range between about -20°C to about 50°C, preferably between -10°C to 20°C. If V, W^1, W^2, Z^1 or Z^2 contains a reactive group toward the reagents used in this transformation, it is necessary to protect such a group prior to this transformation and deprotect at the appropriate time.



145

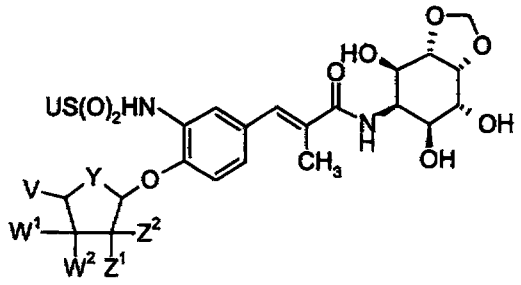
The compound of formula 1 in which $X=NH_2$ (compound **103**) is converted to the corresponding compound of formula **145**, wherein UC(O)NH- is an amide prodrug as described in the detailed description of the invention, by reacting **1**, in the presence of excess base, such as triethylamine or pyridine, with (a) an anhydride compound of the formula, $(UC(O))_2O$, or (b) an acylating agent of the formula, UC(O)L, wherein L is chloro, bromo or

imidazole. UC(O)- may also be an N-protected amino acid residue or a polypeptide chain of two or more (e.g., two, three, or four) amino acid residues. For protection of the amino group a CBZ group or t-BOC group can be utilized (see *Protective Groups in Organic Synthesis*, T. Greene and P. Wuts, Ed., John Wiley & Sons Ltd., New York, 1991). The reaction is stirred in an aprotic solvent, such as tetrahydrofuran, at a temperature range between about -20°C to about 50°C, preferably about -10°C to 20°C. The same transformation can be effected by treating a compound of structure 1 with a carboxylic acid of formula UC(O)OH in the presence of a coupling agent such as DCC, EDCI, or EEDQ. If V, W^1, W^2, Z^1 or Z^2 contains a reactive group toward the reagents used in this transformation, it is necessary to protect such a group prior to this transformation and deprotect at the appropriate time.



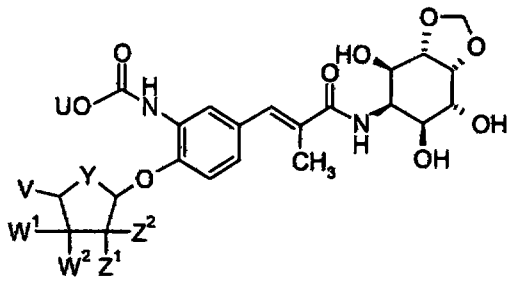
146

The compound of formula 1 in which X=NH_2 (compound **103**) is converted to the corresponding compound of formula **146**, wherein $(UO)_2PONH$- is a phosphoramide prodrug as described in the detailed description of the inventio, by reacting 1, in the presence of excess base, such as triethylamine or pyridine, with (a) a compound of the formula, $((UO)_2PO)_2O$, or (b) a phosphorylating agent of the formula, $(UO)_2P(O)L$, wherein L is chloro or bromo. The same transformation may be effected by treating the compound of structure 1 where X = NH_2 with a reagent of formula $(UO)_2P(O)OH$ in the presence of a coupling agent such as DCC or EDCI. If V, W^1, W^2, Z^1 or Z^2 contains a reactive group toward the reagents used in this transformation, it is necessary to protect such a group prior to this transformation and deprotect at the appropriate time. For example, a primary or secondary amino group might be protected as its 9-fluorenylmethyl, benzyloxycarbonyl or tert-butoxycarbonyl carbamate. A carboxylic acid can be protected as an ester (see *Protective Groups in Organic Synthesis*, T. Greene and P. Wuts, Ed., John Wiley & Sons Ltd., New York, 1991 or *Protecting Groups*, P. Kocienski, Ed., Thieme Medical Publishers, New York, 1994).



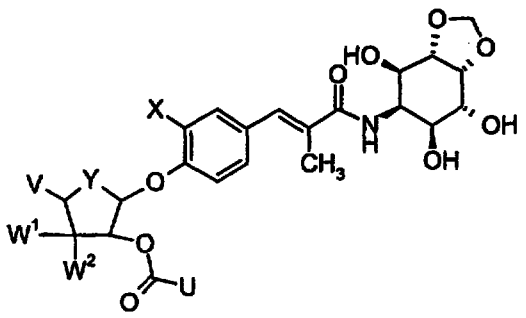
147

The compound of formula **1** in which X=NH_2 (compound **103**) is converted to the corresponding compound of formula **147**, wherein $US(O)_2NH$- is a sulfonamide prodrug as described in the detailed description of the invention, by reacting **1**, in the presence of excess base, such as triethylamine or pyridine, with a compound of the formula, $(US(O)_2)_2O$, or (b) $US(O)_2L$, wherein L is chloro or bromo. The reaction is stirred in an aprotic solvent, such as tetrahydrofuran, at a temperature range between about -20°C to about 50°C, preferably between -10°C to 20°C. If V, W^1, W^2, Z^1 or Z^2 contains a reactive group toward the reagents used in this transformation, it is necessary to protect such a group prior to this transformation and deprotect at the appropriate time.



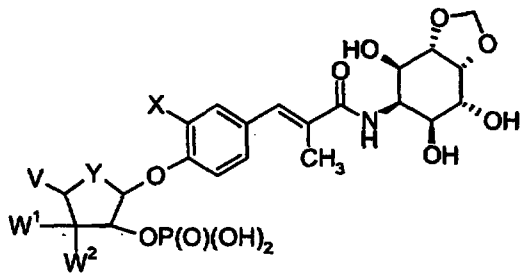
148

The compound of formula **1** where X = NH_2 is converted to the corresponding compound of formula **148**, wherein UOC(O)NH- is a carbamate prodrug as described in the detailed description of the invention, by reacting **1**, in the presence of excess base, such as triethylamine or pyridine, with chloroformate UOC(O)Cl. The reaction is stirred in an aprotic solvent, such as tetrahydrofuran, at a temperature range between about -20°C to about 50°C, preferably between -10°C to 20°C. If V, W^1, W^2, Z^1 or Z^2 contains a reactive group toward the reagents used in this transformation, it is necessary to protect such a group prior to this transformation and deprotect at the appropriate time.



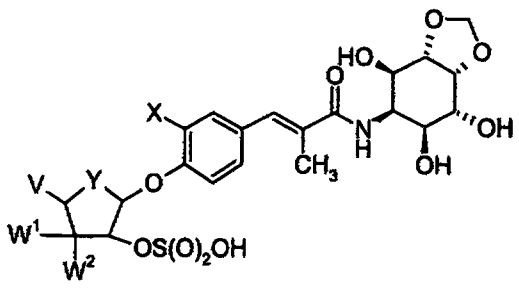
149

Compound **149**, wherein UC(O)O- is an ester prodrug as described in the detailed description of the invention, may be prepared from compound **116** where X is H or protected OH. Conditions similar to those used in the preparation of **145** can be employed. Alternatively, compound **149** may be prepared from compounds **29, 69, 95** or **96** where Z^1 is H and Z^2 is OH. Introduction of the prodrug moiety using conditions similar to those described for preparation of **145** provides the functionalized furanose, which may be elaborated as described in earlier sections to provide **149**. If V, W^1 or W^2 contains a reactive group toward the reagents used in this transformation, it is necessary to protect such a group prior to this transformation and deprotect at the appropriate time.



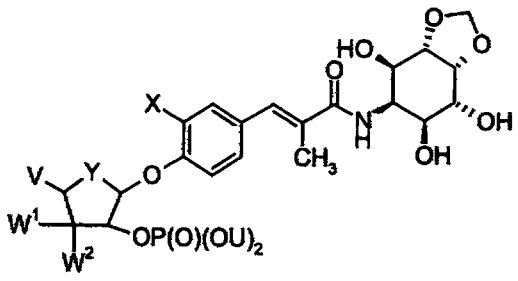
150

Compound **150** may be prepared from compound **116** where X is H or protected OH. Conditions similar to those used for the preparation of **139** can be employed. Alternatively, compound **150** may be prepared from compounds **29, 69, 95** or **96** where Z^1 is H and Z^2 is OH. Introduction of the prodrug moiety using conditions similar to those described for preparation of **139** provides the functionalized furanose, which may be elaborated as described in earlier sections to provide **150**. If V, W^1 or W^2 contains a reactive group toward the reagents used in this transformation, it is necessary to protect such a group prior to this transformation and deprotect at the appropriate time.



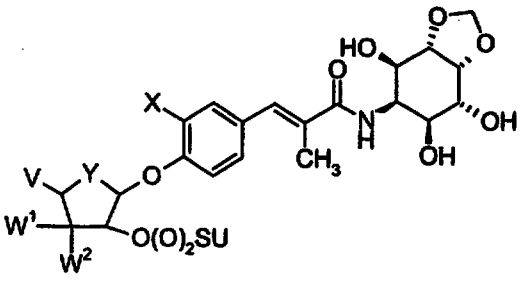
151

Compound **151** may be prepared from compound **116** where X is H or protected OH. The conditions similar to the preparation of **140** can be employed. Alternatively, compound **151** may be prepared from compounds **29**, **69**, **95** or **96** where Z^1 is H and Z^2 is OH. Introduction of the prodrug moiety using conditions similar to those described for preparation of **151** provides the functionalized furanose, which may be elaborated as described in earlier sections to provide **151**. If V, W^1 or W^2 contains a reactive group toward the reagents used in this transformation, it is necessary to protect such a group prior to this transformation and deprotect at the appropriate time.



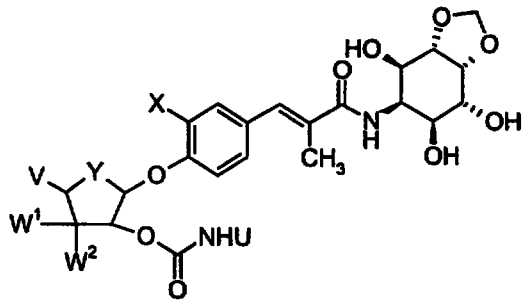
152

Compound **152**, wherein $(UO)_2P(O)O$- is a phosphate prodrug as defined in the description of the invention, may be prepared from compound **116** where X is H or protected OH. Conditions similar to the preparation of **141** can be employed. Alternatively, compound **152** may be prepared from compounds **29**, **69**, **95** or **96** where Z^1 is H and Z^2 is OH. Introduction of the prodrug moiety using conditions similar to those described for preparation of **141** provides the functionalized furanose, which may be elaborated as described in earlier sections to provide **152**. If V, W^1 or W^2 contains a reactive group toward the reagents used in this transformation, it is necessary to protect such a group prior to this transformation and deprotect at the appropriate time.



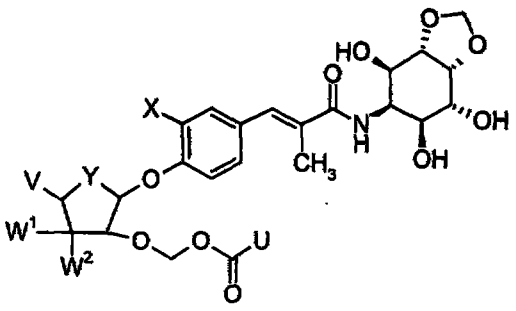
153

Compound **153**, wherein $US(O)_2O$- is a sulfonate prodrug as described in the detailed description of the invention, may be prepared from compound **116** where X is H or protected OH. Conditions similar to the preparation of **142** can be employed. Alternatively, compound **153** may be prepared from compounds **29**, **69**, **95** or **96** where Z^1 is H and Z^2 is OH. Introduction of the prodrug moiety using conditions similar to those described for preparation of **142** provides the functionalized furanose, which may be elaborated as described in earlier sections to provide **153**. If V, W^1 or W^2 contains a reactive group toward the reagents used in this transformation, it is necessary to protect such a group prior to this transformation and deprotect at the appropriate time.



154

Compound **154**, wherein UNHC(O)O- is a carbamate prodrug as described in the detailed description of the invention, may be prepared from compound **116** where X is H or protected OH. Conditions similar to those used in the preparation of **143** can be employed. Alternatively, compound **154** may be prepared from compounds **29**, **69**, **95** or **96** where Z^1 is H and Z^2 is OH. Introduction of the prodrug moiety using conditions similar to those described for preparation of **143** provides the functionalized furanose, which may be elaborated as described in earlier sections to provide **154**. If V, W^1 or W^2 contains a reactive group toward the reagents used in this transformation, it is necessary to protect such a group prior to this transformation and deprotect at the appropriate time.

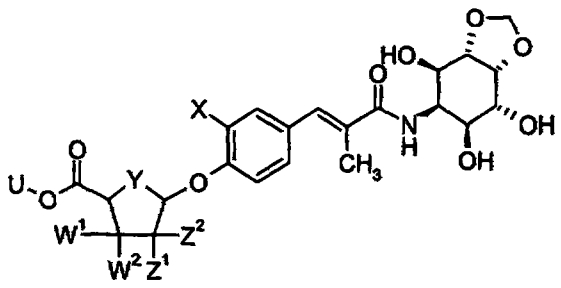


155

Compound **155**, wherein $UC(O)OCH_2O$- is an acyloxymethyl prodrug as described in the detailed description of the invention, may be prepared from compound **116** where X is H or protected OH. Conditions similar to those used in the preparation of **143** can be employed. Alternatively, compound **155** may be prepared from compounds **29, 69, 95** or **96** where Z^1 is H and Z^2 is OH. Introduction of the prodrug moiety using conditions similar to those described for preparation of **143** provides the functionalized furanose, which may be elaborated as described in earlier sections to provide **155**. If V, W^1 or W^2 contains a reactive group toward the reagents used in this transformation, it is necessary to protect such a group prior to this transformation and deprotect at the appropriate time.

Similarly, intermediates **18, 19, 26, 81, 86, 87** or **29, 69, 95, 96** where W^1 is H and W^2 is OH can be derivatized to incorporate an appropriate group and subsequently elaborated into the corresponding prodrugs modified at C3' (at W^1 or W^2). Intermediates **21, 30, 37, 42,** and **44** can be derivatized to incorporate an appropriate group and subsequently elaborated into the corresponding prodrugs modified at V.

When V, W^1, W^2, Z^1 or Z^2 contains a primary or secondary amino group, it can be converted to a prodrug using the procedures described for compounds **145, 146, 147** and **148.**



156

Compound **156**, wherein UOC(O)- is an ester prodrug as described in the detailed description of the invention, may be prepared from compounds **112** and **123**. Reaction of alcohol UOH with **112** or **123** in the presence of a coupling reagent such as DCC, EDCI, or EEDQ in dichloromethane or DMF at temperature ranging from 0°C to 25°C provides

compound **156**. Alternatively, U-L where L is chloro or bromo can be treated with **112** or **123** in the presence of Na_2CO_3 or K_2CO_3 in DMF (*Chem. Pharm. Bull.*, **1984**, 2241). In the case where X, W^1, W^2, Z^1 or Z^2 contains a reactive group under the conditions employed for this transformation, it needs to be protected prior to this transformation and deprotected at the appropriate time (see *Protective Groups in Organic Synthesis*, T. Greene and P. Wuts, Ed., John Wiley & Sons Ltd., New York, 1991 or *Protecting Groups*, P. Kocienski, Ed., Thieme Medical Publishers, New York, 1994). Alternatively, intermediate **32** can be derivatized to incorporate the U group and be elaborated into compound **156** following the chemistry described in the earlier section.

The compounds of the present invention have asymmetric carbon atoms. Compounds having a mixture of isomers at one or more centers will exist as diastereomeric mixtures, which can be separated into their individual diastereomers on the basis of their physical chemical differences by methods known to those skilled in the art, for example, by chromatography or fractional crystallization. All such isomers, including diastereomer mixtures, are considered as part of the invention.

The compounds of the present invention that are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate the compound of the present invention from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the basic compounds of this invention are readily prepared by treating the basic compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is readily obtained. The desired acid salt can also be precipitated from a solution of the free base in an organic solvent by adding to the solution an appropriate mineral or organic acid.

Those compounds of the present invention that are acidic in nature, are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the acidic compounds of the present invention. Such non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium, calcium and magnesium, etc. These salts can easily be prepared by

treating the corresponding acidic compounds with an aqueous solution containing the desired alkali metal alkoxide or metal hydroxide, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide or metal hydroxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum yields of the desired final product.

The antibacterial activity of the compounds of the present invention against bacterial pathogens is demonstrated by the compound's ability to inhibit growth of defined strains of pathogens.

Assay

The assay, described below, employs conventional methodology and interpretation criteria and is designed to provide direction for chemical modifications that may lead to compounds with antibacterial activity against susceptible and drug-resistant organisms including, but not limited to, beta-lactam, macrolide and vancomycin resistance. In the assay, a panel of bacterial strains is assembled to include a variety of target pathogenic species, including representatives of antibiotic resistant bacteria. Use of this panel enables the chemical structure/activity relationship to be determined with respect to potency and spectrum of activity. The assay is performed in microtiter trays and interpreted according to Performance Standards for Antimicrobial Disk Susceptibility Tests - Sixth Edition; Approved Standard, published by The National Committee for Clinical Laboratory Standards (NCCLS) guidelines; the minimum inhibitory concentration (MIC) is used to compare strains. Compounds are initially dissolved in dimethylsulfoxide (DMSO) as stock solutions.

The activity of the compounds of the present invention also may be assessed in accord with Steers replicator technique which is a standard in vitro bacterial testing method described by Steers et al., *Antibiotics and Chemotherapy* **1959**, 9, 307.

The in vivo activity of the compounds of the present invention can be determined by conventional animal protection studies well known to those skilled in the art, usually carried out in rodents.

According to one *in vivo* model, compounds are evaluated for efficacy in mouse models of acute bacterial infection. An example of one such *in vivo* system is provided as follows. Mice (CF1 mixed sex mice; 18-20 g) are allotted to cages upon their arrival, and allowed to acclimate 1-2 days before being placed in a study. The acute infection is produced by intraperitoneal inoculation of bacteria (*Staphylococcus aureus* strain 01A1095) suspended in 5% sterile hog gastric mucin. The inoculum is prepared by: growing the culture overnight at 37°C on blood agar, harvesting the resulting surface growth with sterile brain heart infusion

broth, and adjusting this suspension to a turbidity that when diluted 1:10 into 5% sterile hog gastric mucin would produce 100% lethality.

Mice (10 per group) are treated subcutaneously, at 0.5 hour and 4 hours after challenge. Appropriate non-treated (infected but not treated) and positive (vancomycin or minocycline, etc.) controls are included in each study. Percent survival is recorded after a 4-day observation period; the PD_{50} (mg/kg/dose calculated to protect 50% of infected animals) is determined by the probit method.

The compounds of the present invention, and the pharmaceutically acceptable salts thereof (hereinafter "the active compounds"), may be administered through oral, parenteral, topical, or rectal routes in the treatment of bacterial and protozoal infections. In general, these compounds are most desirably administered in dosages ranging from about 0.2 mg per kg body weight per day (mg/kg/day) to about 200 mg/kg/day in single or divided doses (i.e., from 1 to 4 doses per day), although variations will necessarily occur depending upon the species, weight and condition of the subject being treated and the particular route of administration chosen. However, a dosage level that is in the range of about 3 mg/kg/day to about 60 mg/kg/day is most desirably employed. Variations may nevertheless occur depending upon the species of mammal, fish or bird being treated and its individual response to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effects, provided that such larger doses are first divided into several small doses for administration throughout the day.

The active compounds may be administered alone or in combination with pharmaceutically acceptable carriers or diluents by the routes previously indicated, and such administration may be carried out in single or multiple doses. More particularly, the active compounds may be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the active compounds are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch),

alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral adinistration, the active compound may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For parenteral administration, solutions of an active compound in either sesame or peanut oil or in aqueous ethanol or propylene glycol may be employed. Use of a cyclodextrin derivative such as β-cyclodextrin sulfobutyl ether, sodium salt (see United States patent 5,134,127) may also be advantageous. The aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques known to those skilled in the art.

Additionally, it is also possible to administer the active compounds of the present invention topically and this may be done by way of creams, jellies, gels, pastes, patches, ointments and the like, in accordance with standard pharmaceutical practice.

For administration to animals other than humans, such as cattle or domestic animals, the active compounds may be administered in the feed of the animals or orally as a drench composition.

The active compounds may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

The active compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide phenyl, polyhydroxyethylaspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the active compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters,

polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

The present invention is further described and exemplified in the preparations and examples described below. In the preparations and examples, "rt" means room or ambient temperature which is a temperature within the range of about 20-25°C.

Experimental procedures

Experimental Procedures For Examples

In cases where final purification was effected using silica gel chromatography with an eluant system containing more than 10% methanol, the chromatographed product was taken up in 89:10:1 chloroform: methanol: concentrated ammonium hydroxide and filtered, or dissolved in methanol and passed through a 0.45 μM filter. Removal of solvent *in vacuo* provided the final product.

Purifications were generally carried out by silica gel chromatography. When crude products were insoluble in the chloroform/methanol eluant system, they were generally preadsorbed onto silica gel through addition of dry silica gel to a methanol solution of the product, followed by complete removal of solvent. When crude products were insoluble in the ethyl acetate/hexanes eluant system, they could be loaded as solutions in dichloromethane. Column elution in many cases was run as a step gradient.

Preparation of hydroxylamine reagents for synthesis of oxime ethers

The hydroxylamine reagents employed were either commercially available (generally as an acid salt), or prepared from the corresponding alcohol or halide via the methods outlined below:

1) Preparation of phthalimide-protected hydroxylamines:

From the alcohol:

A Mitsunobu reaction with diethyl azodicarboxylate and triphenylphosphine was used to couple N-hydroxyphthalimide and the alcohol starting material (*Synthesis*, **1976**, 682).

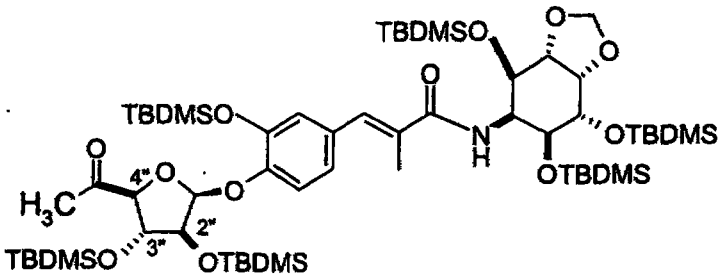
From the bromide or chloride:

Reaction of N-hydroxyphthalimide (1 equivalent) with the halide starting material (1.2 - 2 equivalents) was carried out in DMSO solution, using potassium carbonate (0.6 - 2 equivalents) as base. The reactions were carried out at room temperature, generally by stirring overnight. Pouring the reaction mixture into cold water provided a precipitate, which was filtered to give the phthalimide-protected hydroxylamine. In many cases, this material was directly deprotected; silica gel chromatography can also be employed, using ethyl acetate-hexane mixtures, to purify the phthalimide-protected hydroxylamine.

2) Removal of the phthalimide protecting group to provide the hydroxylamine:

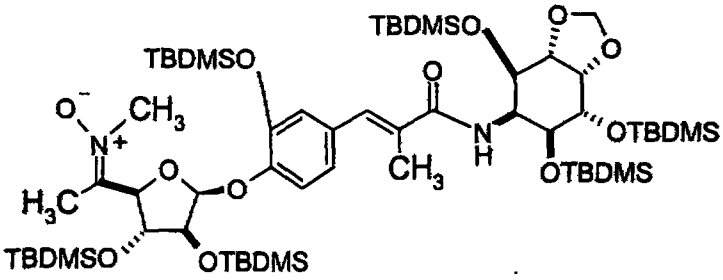
Deprotection of the phthalimide-protected hydroxylamine was effected by reaction with hydrazine hydrate (1 - 2 equivalents) in ethanol solution, at temperatures ranging from room temperature to reflux, for periods ranging from 30 minutes to overnight. The reaction mixture was filtered, and the filtrate concentrated. This crude product can be taken to the next step as is, or can be further purified. Mixing the crude product with chloroform, removing solids by filtration and removal of solvent from the filtrate removes additional phthalhydrazide. Alternatively, the crude product was dissolved in 1N hydrochloric acid, and washed with ether or ethyl acetate. The aqueous layer was basified with saturated potassium carbonate solution and extracted with ether or ethyl acetate. Drying of the final organic layers and removal of solvent provided the hydroxylamine product. N-Methyl-O-benzylhydroxylamine was prepared according to the procedure reported in *J. Org. Chem.*, **1981**, *46*, 5438.

Preparation of Examples 1 - 6



A1

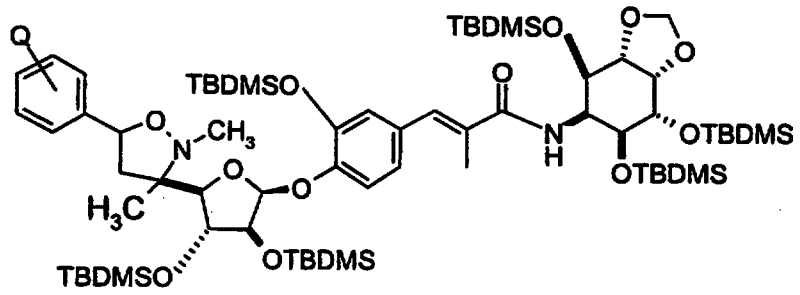
A solution of hygromycin A, tert-butyldimethylsilyl chloride (12 equivalents), and imidazole (12 equivalents) in DMF (hygromycin concentration 0.25 M) was stirred at 80°C for 20 hours. After removal of the DMF under reduced pressure, the resulting residue was diluted with water and extracted with diethyl ether. The combined ether extracts were washed with water, then saturated sodium chloride solution, dried over sodium sulfate, filtered, and concentrated. The crude product was purified by silica gel chromatography, eluting with 10% ethyl acetate/ hexanes.



A2

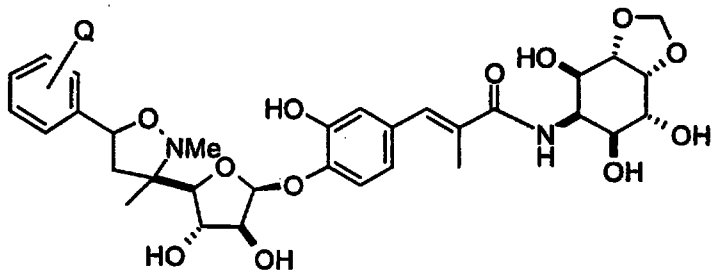
Compound **A1** was dissolved in ethanol (0.1 M) and treated with methylhydroxylamine hydrochloride (1.5 equivalents) and sodium acetate (2.5 equivalents).

The reaction mixture was stirred at room temperature for 18 hours, then poured into water. This mixture was treated with saturated sodium bicarbonate solution until the pH rose to 8, then extracted with chloroform. The combined organic layers were dried over magnesium sulfate and concentrated to provide **A2**.



A3

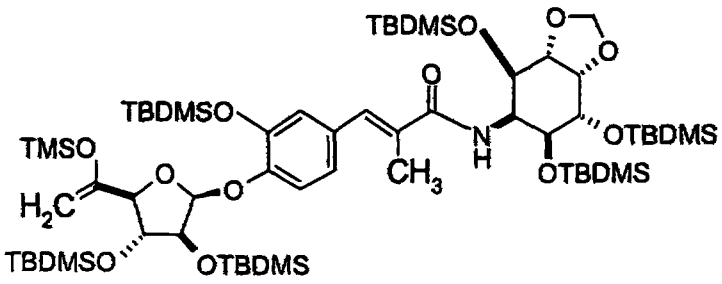
A solution of **A2** in toluene (0.15 - 0.18 M) was treated with the appropriate styrene (3 equivalents) and the reaction mixture heated at reflux for 18 – 72 hours, until thin layer chromatography indicated that most of the starting material had been consumed. Removal of solvent *in vacuo* and purification by silica gel chromatography using 3 – 15% ethyl acetate in hexane provided the product **A3**. In some cases, both diastereomers around the phenyl group could be isolated.



A4

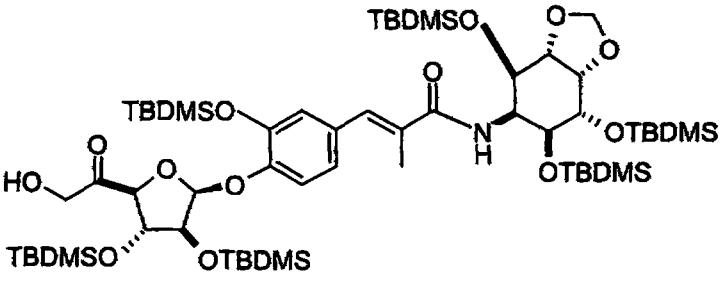
A solution of **A3** in tetrahydrofuran (0.1 M) was treated with two volumes of an 8:2:1 mixture of tetrahydrofuran:pyridine:70% HF in pyridine, and allowed to stir at room temperature for one to four days, until tlc indicated the reaction had substantially progressed. Solid sodium bicarbonate was added, giving a thick slurry, which was diluted with ethyl acetate and treated with additional sodium bicarbonate until gas evolution had ceased. The mixture was filtered, and the filtrate concentrated and purified by silica gel chromatography (eluant: 3 – 20% methanol in chloroform) to provide the compounds of Examples 1 - 6.

Preparation of Examples 7 - 11



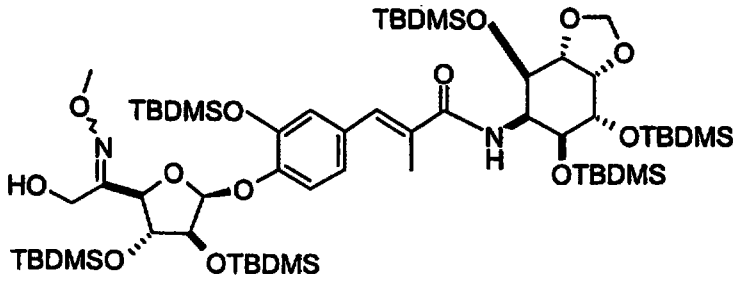
A5

A solution of persilyl hygromycin **A1** was dissolved in methylene chloride (0.06 M), treated with triethylamine and cooled to –50°C. Trimethylsilyl triflate (10 equivalents) was added dropwise over 15 minutes. After 5 hours, the reaction was quenched by addition of saturated ammonium chloride solution. The organic layer was concentrated *in vacuo*, and the residue was dissolved in ethyl acetate, washed with water, dried over sodium sulfate and concentrated *in vacuo* to provide crude **A5**, which was used without further purification.



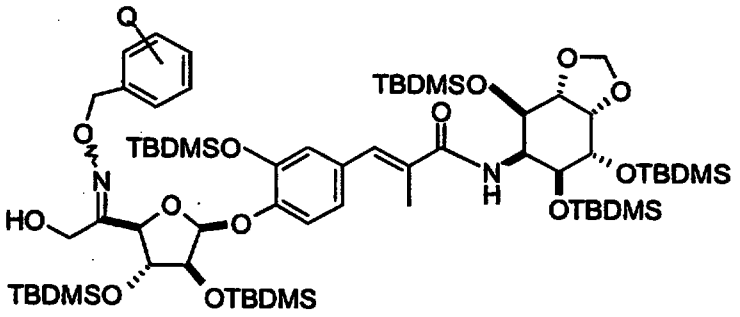
A6

A solution of **A5** in dichloromethane (0.1 M) was treated with m-chloroperbenzoic acid (1.1 equivalents) and allowed to stir at room temperature for 24 hours. The solvent was removed *in vacuo*, and the residue was dissolved in THF (0.2 M), and treated with hydrochloric acid (0.2 N, equal volume). After 4.5 hours at room temperature, the reaction was treated with saturated sodium bicarbonate solution, and concentrated *in vacuo*. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried over sodium sulfate, filtered and concentrated to provide crude **A6**. Purification was carried out by silica gel chromatography (eluant: 3 – 10% ethyl acetate in hexanes).



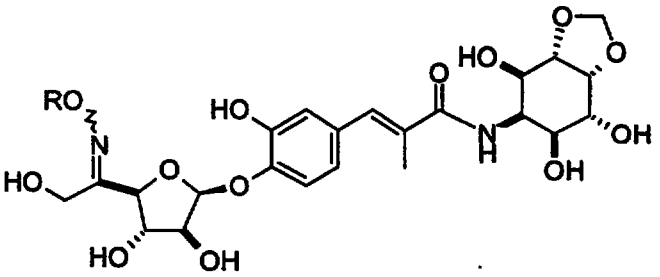
A7

A solution of compound **A6** in methanol (0.04 M) was treated with N-methyl hydroxylamine hydrochloride (2.3 eq.) and potassium carbonate (1.0 eq.) and allowed to react at room temperature for 18 hours. The solvent was removed *in vacuo* and the residue purified by silica gel chromatography (eluant: 5% 1- 20% ethyl acetate in hexanes). Product **A7** was obtained as a mixture of E and Z isomers around the oxime ether.



A8

A solution of **A6** in methanol (0.05 - 0.1M) was treated with the benzyl hydroxylamine (2 eq.) and allowed to stir at room temperature for 18 - 72 hours. In some cases, triethylamine hydrochloride (1.1 eq.) was used in the reaction. The solvent was removed *in vacuo*, and the crude material (a mixture of E and Z isomers around the oxime ether) was purified by silica gel chromatography (eluant, 5% - 15% ethyl acetate in hexanes).

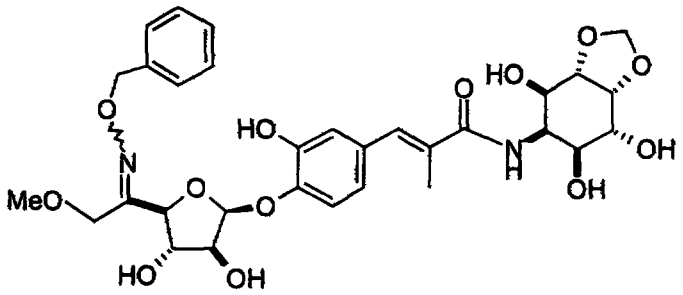


A9

Removal of the silyl protecting groups from compound **A7** and **A8** was carried out by treating a solution of **A7** or **A8** in THF with pyridine and 70% HF in pyridine such that the final

concentration of substrate was 0.01 M, and the solvent composition was 8:2:1 tetrahydrofuran:pyridine:70% HF in pyridine. The reaction mixture was stirred at room temperature for up to 5 days, until tlc indicated that the reaction had substantially progressed to product. In some cases, the reaction mixture was heated at 45°C for 4.5 hours, then at room temperature for 48 hours. Solid sodium bicarbonate was added, and the mixture was filtered. Concentration of the filtrate gave crude product, which was purified by silica gel chromatography (eluant 3 - 10% methanol in chloroform). Product **A9** was obtained as a mixture of E and Z isomers around the oxime ether.

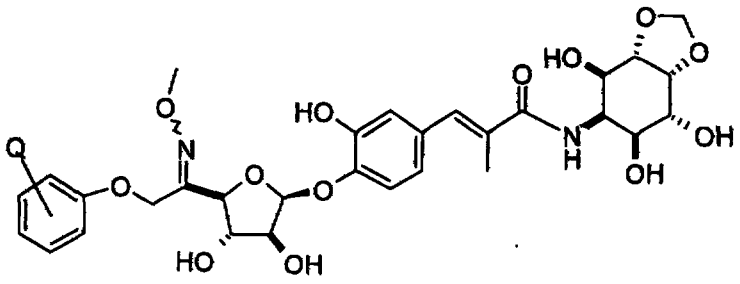
Preparation of Example 12



A10

Compound **A6** was converted to its benzyl oxime ether by the procedure described for preparation of **A8**. This oxime ether was dissolved in THF (0.1 M) and treated with sodium hydride (1.2 eq.), followed by addition of methyl iodide (4 eq.). The reaction was allowed to stir for 18 hours at room temperature. Saturated aqueous ammonium chloride was added to the reaction, and volatiles were removed *in vacuo*. The aqueous mixture was extracted with chloroform, and the combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification was effected via silica gel chromatography, eluting with 5% to 6% ethyl acetate in hexanes. Removal of the silyl groups was carried out as described for preparation of **A9**, to provide the compound of Example 12.

Preparation of Examples 13 - 15



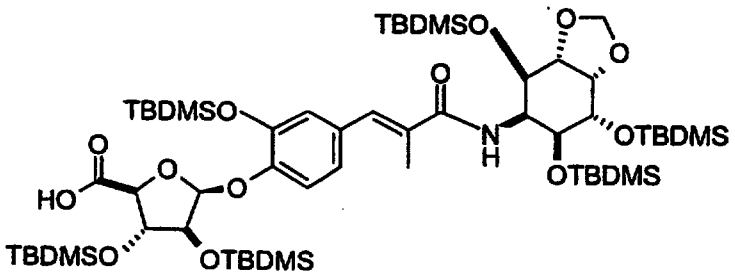
A11

A solution of **A7** (0.1 - 0.5 M) and the phenol reagent (2.7 eq.) in toluene was treated with triphenylphosphine (2.7 eq.) and diethyl azodicarboxylate (2.5 eq.). After 18 hours, the

reaction was diluted with ethyl acetate and washed with phosphate buffer (pH 7). The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with saturated sodium chloride solution and dried over magnesium sulfate. Removal of solvent *in vacuo* gave a crude product which was purified by column chromatography (1% to 20% ethyl acetate in hexanes) to provide the α-phenoxy oxime ether.

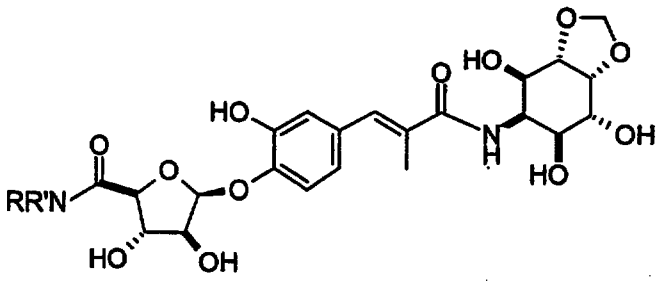
Removal of the silyl protecting groups was carried out by treating a solution of the protected α-phenoxy oxime ether in THF with pyridine and 70% HF in pyridine such that the final concentration of substrate was 0.01 M, and the solvent composition was 8:1:1 tetrahydrofuran:pyridine:70% HF in pyridine. The reaction was allowed to stir at room temperature for 18 hours. Solid sodium bicarbonate was added, giving a thick slurry, which was diluted with ethyl acetate and treated with additional sodium bicarbonate until gas evolution had ceased. The mixture was filtered, and the filtrate concentrated and purified by silica gel chromatography (eluant: 3 – 10% methanol in chloroform) to provide the compounds of Examples 13 - 15 as a mixture of E and Z isomers around the oxime ether.

Preparation of Examples 16 - 22



A12

Compound **A6** was dissolved in benzene (0.05 M) and treated with water (2 eq) and lead tetraacetate (1.0 eq.). After 2 hours at room temperature, water was added to the reaction, and the mixture was extracted with ethyl acetate. The combined organic layers were washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated *in vacuo*. This material can be used directly in further reactions, or be purified by silica gel chromatography (eluant: 5% to 10%, then 75% ethyl acetate in hexanes).

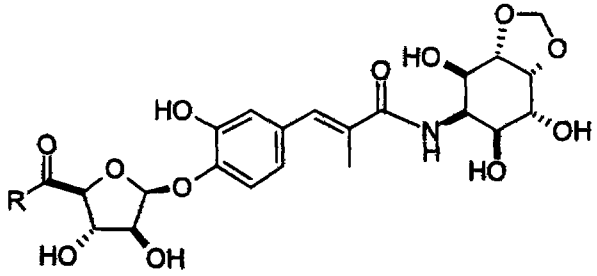


A13

Compound **A12** was dissolved in methylene chloride (0.1 - 0.15 M) and treated with the appropriate amine or hydroxylamine (1.1 - 1.5 eq.), 1-hydroxybenzotriazole (2 eq.) and triethylamine (1 eq.). After addition of EDC (1 eq), the reaction was allowed to stir for 4-24 hours at room temperature. The reaction was then quenched by addition of water; the layers were separated and the aqueous layer was extracted with additional methylene chloride. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to provide the crude product. Purification was effected by silica gel chromatography (6% - 13% ethyl acetate in hexanes) to provide the persilylated amide or hydroxamate.

Removal of the silyl protecting groups was carried out using the same procedure as above for preparation of compound **A4**, to provide the compounds of Examples 16 - 22.

Preparation of Examples 23 - 25



A14

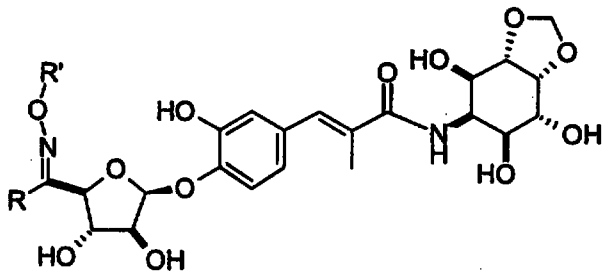
Compound **A12** was dissolved in THF (0.2 M) and treated with carbonyl diimidazole (3 eq.). After 1 hour at room temperature, an equal volume of methylene chloride was added, followed by triethylamine (10 eq.) and N,O-dimethylhydroxylamine hydrochloride (5 eq.). The reaction was allowed to stir at ambient temperature for 1.5 hours, then poured into water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to give crude Weinreb amide. Purification was carried out by silica gel chromatography (eluant: 10% ethyl acetate in hexanes).

The Weinreb amide was dissolved in THF (0.4 - 0.8 M), cooled to 0°C, and treated with the appropriate Grignard reagent or organolithium reagent (1 - 6 eq.). The reaction mixture was allowed to warm to room temperature. After 3-4 hours the reaction mixture was poured into 0.01-0.1 N aqueous HCl and extracted with ethyl acetate. The combined organic layers were washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated to provide the crude ketone. Purification was carried out by silica gel chromatography (eluant: 7% - 10% ethyl acetate in hexanes).

Removal of the silyl protecting groups was carried out by dissolving the ketone product in tetrahydrofuran (0.1 M) and treating it with 2 - 5 volumes of an 8:1:1 mixture of tetrahydrofuran:pyridine:70% HF in pyridine. The reaction was allowed to stir at room temperature for one to four days, until tlc indicated the reaction had substantially progressed.

Solid sodium bicarbonate was added, giving a thick slurry, which was diluted with methanol and filtered. Concentration of the filtrate gave a residue which was purified by silica gel chromatography (eluant: 5% – 15% methanol in chloroform) to provide the compounds of Examples 23 - 25.

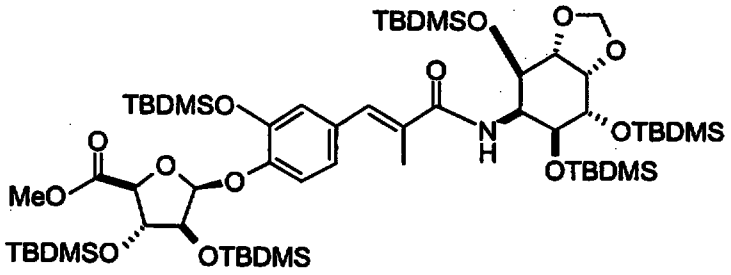
Preparation of Examples 26 - 31



A15

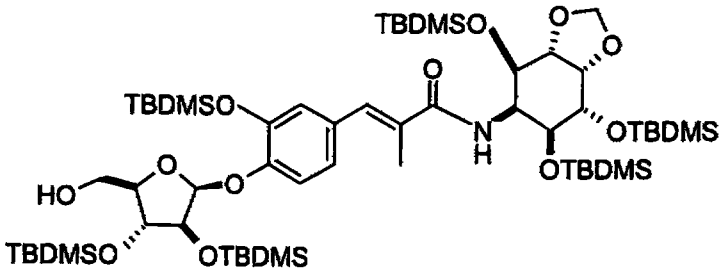
Ketone **A14** was dissolved in methanol (0.02 - 0.1 M), treated with the appropriate hydroxylamine (3 eq.) and stirred at room temperature for 18 hours. In the case of the p-fluorophenyl ketone, the reaction was carried out at 50°C for 10 hours. The reaction was then adsorbed onto silica gel and purified by silica gel chromatography (eluant 5 - 15% methanol in chloroform), to provide in some cases both E and Z oxime ether isomers of the compounds of Examples 26 - 31.

Preparation of Examples 32 - 36



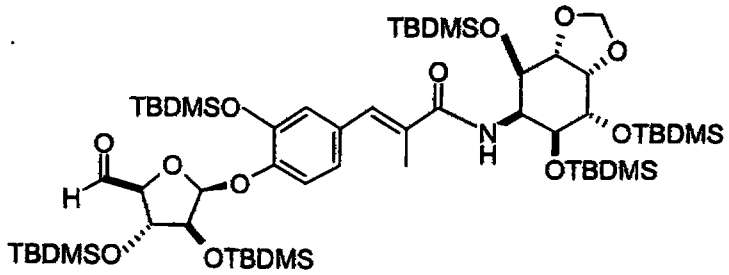
A16

Compound **A6** was dissolved in 2:1 benzene:methanol (0.1 M) and treated with lead tetraacetate (1.5 eq.). After 2 hours at 0°C, saturated sodium bicarbonate solution was added to the reaction. The mixture was filtered and volatiles removed *in vacuo*. The remaining aqueous mixture was extracted with chloroform, and the combined organic layers were dried over sodium sulfate. Filtration and concentration *in vacuo* provided **A16**, which was used without purification.



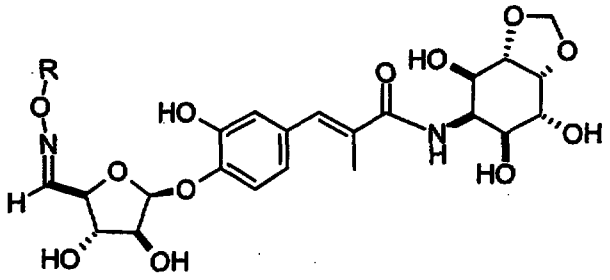
A17

A solution of compound **A16** in THF (0.1 M) was cooled to 0°C and treated with a solution of lithium borohydride in THF (2.0 M, 5 eq.). The reaction was allowed to warm to room temperature. After 48 hours, the reaction was poured into saturated aqueous ammonium chloride solution and extracted with methylene chloride. The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification by silica gel chromatography (eluant: 15% ethyl acetate in hexanes) provided compound **A17**.



A18

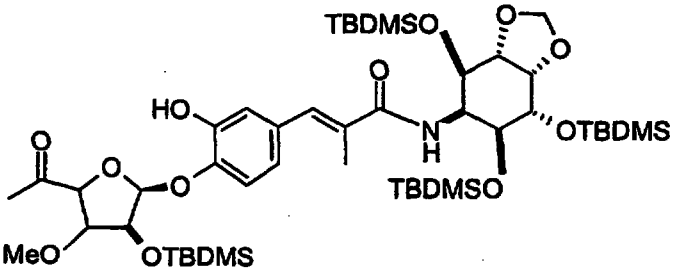
A solution of oxalyl chloride (2 eq.) in methylene chloride (0.15 M) was cooled to -78°C, treated with DMSO (4 eq) in methylene chloride (4.2 M), and allowed to stir for 5 minutes. Compound **A17** (1 eq.) in methylene chloride (0.2 M) was added dropwise at -78°C over 5 minutes. The reaction was stirred an additional 25 minutes at -78°C, then treated with triethylamine (10 eq), ad allowed to warm to room temperature. After 40 minutes, the reaction was poured into water and extracted with methylene chloride. The combined organic layers were washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated. Purification was carried out via silica gel chromatography (eluant: 10% ethyl acetate in hexanes) to provide compound **A18**.



A19

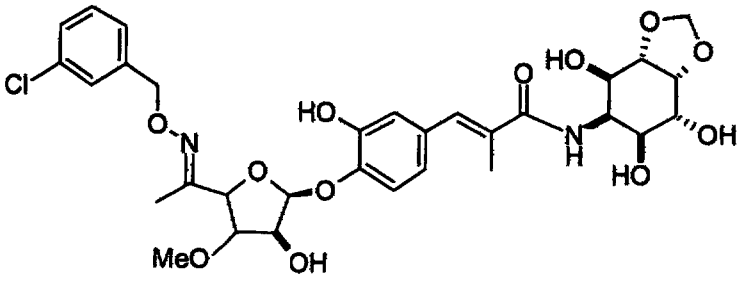
A solution of compound **A18** in methanol (0.06 - 0.15 M) was treated with the appropriate hydroxylamine reagent (2 eq) and triethylamine hydrochloride (1 eq) and stirred at 45-50°C for 2-10 hours. Removal of solvent and purification of the residue by silica gel chromatography (eluant 12% - 15% ethyl acetate in hexanes) gave the persilylated oxime ether. The silyl groups were removed via subjection of this intermediate in tetrahydrofuran (0.1 M) to 2-4 volumes of 8:2:1 tetrahydrofuran:pyridine:70% HF in pyridine. The reaction was allowed to stir at room temperature for 4 days. In some cases, the reaction was heated at 45-50°C for 10 hours, then allowed to stir at room temperature for 8 hours. Solid sodium bicarbonate was added, and the mixture was diluted with THF and methanol and filtered. Purification via silica gel chromatography (eluant: 5% - 15% methanol in chloroform) provided the compounds of Examples 32 - 36 as a mixture of isomers around the oxime ether.

Preparation of Example 37



A20

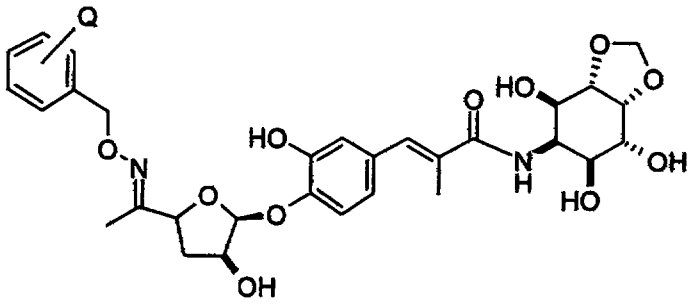
A solution of compound **A1** in methanol (0.1M) was treated with potassium carbonate (1.1 eq.). After 24 hours at room temperature, the reaction was concentrated *in vacuo*, and the residue taken up in phosphate buffer (pH 7). The aqueous mixture was extracted with ethyl acetate, and the combined organic layers were dried over sodium sulfate and evaporated to dryness. Purification was effected via silica gel chromatography (eluant 20% ethyl acetate in hexanes) to provide compound **A20** as a minor product and predominantly one isomer.



A21

A solution of **A20** in methanol (0.15 M) was treated with O-(3-chlorobenzyl)hydroxylamine (1.2 eq.) and allowed to stir at room temperature for 4 days. The solvent was removed *in vacuo*, and the crude material was purified by silica gel chromatography (eluant, 8 % ethyl acetate in hexanes) to provide the silylated benzyl oxime ether. Removal of the silyl groups was carried out as described for preparation of compound **A9**. The compound of Example 37 was obtained as predominantly one isomer.

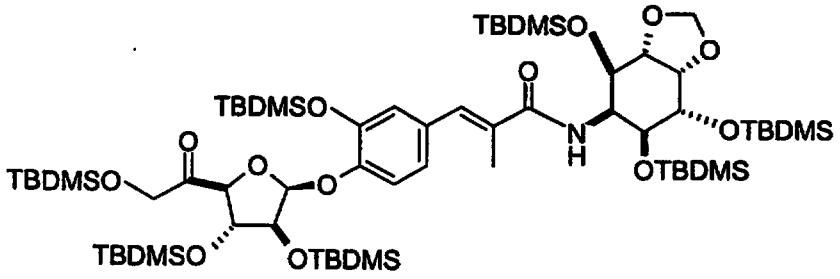
Preparation of Examples 38 and 39



A22

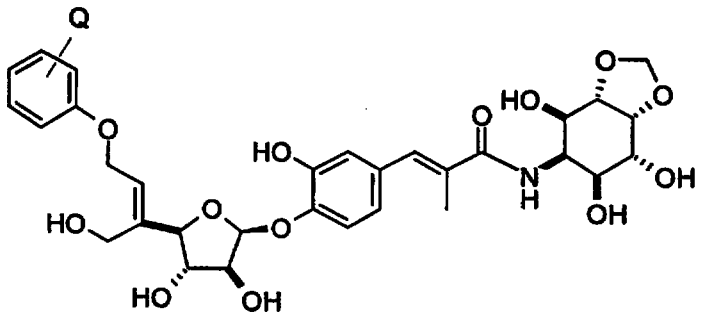
3"-Deoxy hygromycin A, as a mixture of isomers at C-4", was prepared according to the method described in *Bioorg. & Medicinal Chem. Lett.*, **1993**, *3*, 1531. Oxime ether formation was carried out as described in the preparation of compound **A8**, except that 3 equivalents of the hydroxylamine were used. The compounds of Examples 38 and 39 were obtained as E and Z isomers around the oxime center, and as a mixture of isomers at C-4".

Preparation of Example 40



A23

A solution of **A6** (1 eq.) and imidazole (4.9 eq.) in dimethylformamide (0.1 M) was treated with *tert*-butyldimethylsilyl chloride (4.9 eq.) at 60°C and allowed to stir for 2.5 hours. The reaction was cooled to room temperature, diluted with 1:1 hexanes:ether and washed with pH 7.0 phosphate buffer solution (0.05 M), water and finally saturated sodium chloride solution. The organic layer was dried over magnesium sulfate, filtered and concentrated to provide crude **A23**. The crude product was purified by silica gel chromatography, eluting with a step gradient of 2.5% ethyl acetate in hexanes to 20% ethyl acetate in hexanes.



A24

A solution of ethyl (trimethylsilyl)acetate (4 eq.) in THF (roughly 0.4 M in ethyl (trimethylsilyl)acetate) at -78°C was treated with lithium diisopropylamide (3.5 eq.). After 30 minutes a solution of **A23** (1 eq.) in THF (roughly 0.5 M) was added. After 15 minutes the reaction was diluted with ethyl acetate and saturated ammonium chloride solution. The organic layer was washed with saturated ammonium chloride solution, then saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated.

A solution of this crude ethyl ester (1 eq.) in dichloromethane (roughly 0.1M) at -78°C was treated with diisobutyl aluminum hydride (8 eq.). After treatment with saturated Rochelle's salt and warming to room temperature the reaction was diluted with dichloromethane, washed with saturated ammonium chloride, then saturated sodium chloride, dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by

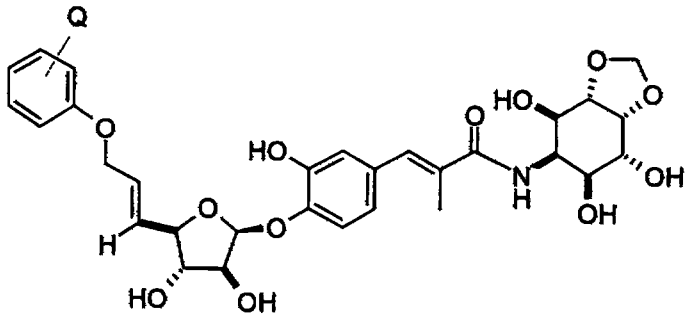
silica gel chromatography, eluting with a step gradient of 5% ethyl acetate in hexanes to 33% ethyl acetate in hexanes to provide pure E allylic alcohol.

Silylated hygromycin allyl alcohol (1 eq.) in toluene (roughly 0.03 M) was treated with the appropiate phenol (3-5 eq.), triphenylphosphine (3-5 eq.) and diethyl azodicarboxylate (3-5 eq). After completion (roughly 30 minutes to 2 hours) the reactions were diluted with ethyl acetate and 0.05 M pH 7.0 phosphate buffer solution. The organic layer was washed with saturated sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated.

Deprotection by the following method provided Example 40:

The silyl groups were removed by treatment of a solution of polysilylated hygromycin A derivative in THF (roughly 0.1M) with a solution of HF•pyridine/pyridine/THF for 20 to 50 hours at room temperature. The reactions were diluted with ethyl acetate, treated with solid $NaHCO_3$, filtered, concentrated and purified by silica gel chromatography, eluting with a step gradient of 5% methanol in dichloromethane to of 33% methanol in dichloromethane.

Preparation of Examples 41-43



A25

A solution of **A18** (1 eq.) and carboethoxymethylene triphenylphosphorane (2.5 eq.) in dimethylformamide (roughly 0.5 M) was allowed to stir at 50°C for 15 hours and allowed to cool to room temperature. The reaction was diluted with hexanes and diethyl ether (roughly 1:1), washed with water, then saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated.

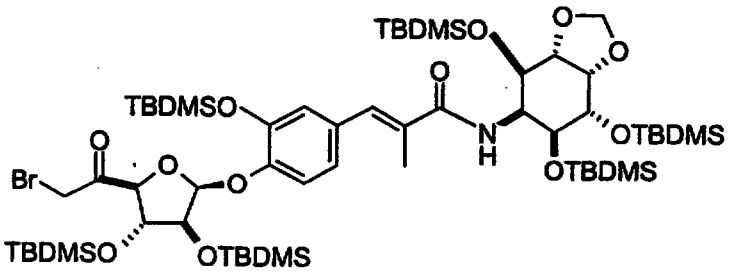
A solution of the crude ethyl ester (1 eq.) in dichloromethane (roughly 0.1M) at -78°C was treated with diisobutyl aluminum hydride (5 eq.). After treatment with saturated Rochelle's salt and warming to room temperature the reaction was diluted with dichloromethane, washed with pH 7.0 phosphate buffer solution (0.05 M), saturated ammonium chloride, saturated sodium chloride, and then dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by silica gel chromatography,

eluting with a step gradient of 5% ethyl acetate in hexanes to 20% ethyl acetate in hexanes to provide pure E allylic alcohol.

Silylated hygromycin allyl alcohol (1 eq.) in toluene (roughly 0.03 M) was treated with the appropiate phenol (3-5 eq.), triphenylphosphine (3-5 eq.) and diethyl azodicarboxylate (3-5 eq). After completion (roughly 30 minutes to 2 hours) the reactions were diluted with ethyl acetate and 0.05 M pH 7.0 phosphate buffer solution. The organic layers were washed with saturated sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated.

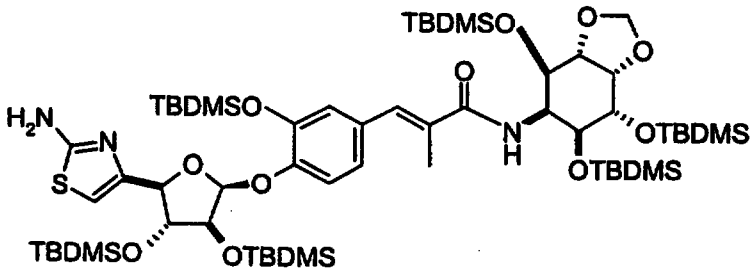
The crude allyl ethers were deprotected and purified by the method used in preparation of compound **A24**, to provide the compounds of Examples 41-43.

Preparation of Example 44



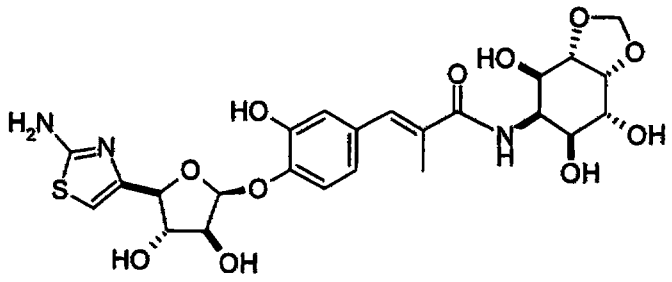
A26

A solution of **A5** (1 eq.) and sodium bicarbonate (2.3 eq.) in tetrahydrofuran (0.1 M) at 4°C was treated with N-bromosuccinimide (2 eq.) in tetrahydrofuran (0.5 M). After 30 minutes the reaction was diluted with ethyl acetate and washed with saturated ammonium chloride, water and saturated sodium chloride and then filtered, concentrated to afford **A26**.



A27

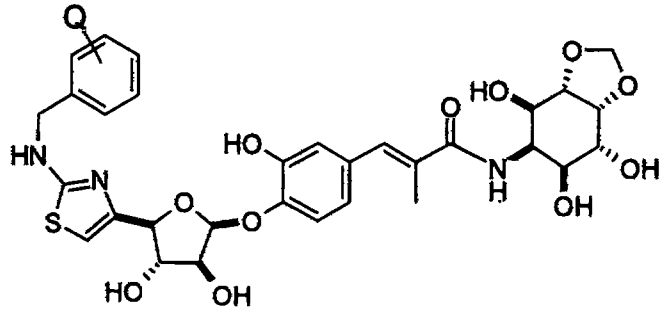
A solution of **A26** (1 eq.) in dimethylformamide (0.1 M) at 4°C was treated with thiourea (2.2 eq.). After completion (1.5 hours) the reaction was diluted with hexanes and diethyl ether (roughly 1:1), washed with pH 7.0 phosphate buffer solution (0.05 M), saturated ammonium chloride, saturated sodium chloride, and then dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by silica gel chromatography, eluting with a step gradient of 10% ethyl acetate in hexanes to 50% ethyl acetate in hexanes.



A28

Compound **A27** was deprotected and purified by the method used in preparation of compound **A24**, to afford **A28**, the compound of Example 44.

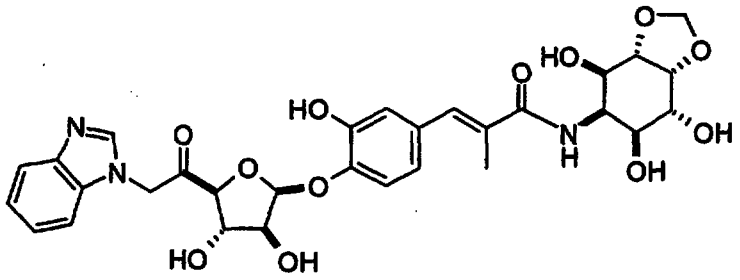
Preparation of Examples 45-47



A29

A solution of **A27** (1 eq.) in toluene (0.05 M) at 70°C was treated with the appropriate benzaldehyde (2-3 eq.). After 15-20 hours the reaction was concentrated, taken up in 3:1 methanol:dichloromethane (0.025 M) and treated with sodium borohydride (5 eq.). After 15 to 30 minutes the reaction was diluted with dichloromethane and water. Hydrochloric acid (1M) was added until the pH of the aqueous layer was 7. The layers were separated and the organic layer washed with water and saturated sodium chloride and then filtered, concentrated. Crude benzyl aminothiazole was deprotected and purified by the method used in preparation of compound **A24**, to afford **A29**, the compounds of Examples 45-47.

Preparation of Example 49

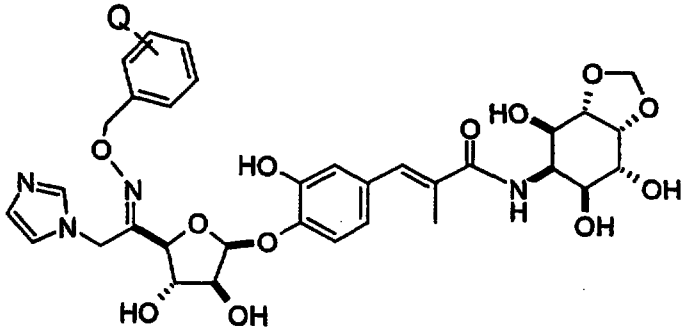


A30

To a solution of **A26** (1 eq.) in 9:1 toluene:dimethylformamide (0.1 M) was added benzimidazole (2.2 eq.). After 18 hours the reaction was diluted with hexanes and diethyl ether (roughly 1:1), washed with saturated ammonium chloride, saturated sodium chloride, and then dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by silica gel chromatography, eluting with a step gradient of 10% ethyl acetate in hexanes to 33% ethyl acetate in hexanes.

Protected **A30** was deprotected and purified by the method used in preparation of compound **A24**, to afford **A30**, the compound of Example 48.

Preparation of Example 49

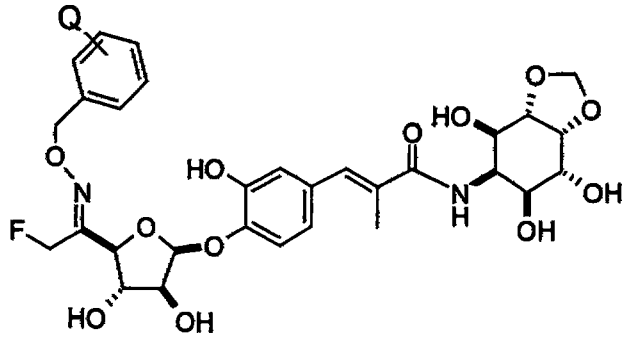


A31

To a solution of **A26** (1 eq.) in toluene (0.1 M) was added imidazole (1.3 eq.). After 16 hours the reaction was diluted with ethyl acetate, washed with pH 7.0 phosphate buffer solution (0.05 M), saturated sodium chloride and then dried over magnesium sulfate, filtered, and concentrated.

Crude ketone was converted to oxime via the chemistry described in preparation of the p-fluorophenyl compound **A15**, until tlc showed the reaction was substantially complete, and deprotected and purified by the method used in preparation of compound **A24**, to afford **A31**, the compound of Example 49.

Preparation of Example 50

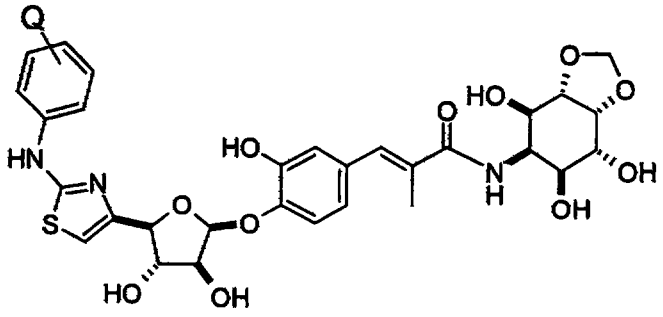


A32

To a solution of **A26** (1 eq.) in dimethylformamide (0.1 M) was added [1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoro-borate) (5 eq.). After 15 hours the reaction was diluted with hexanes and diethyl ether (roughly 1:1), washed with water, saturated sodium chloride and then dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by silica gel chromatography, eluting with a step gradient of 5% ethyl acetate in hexanes to 20% ethyl acetate in hexanes.

Crude ketone was converted to oxime via the chemistry described in preparation of the p-fluorophenyl compound **A15**, until tlc showed the reaction was substantially complete, then deprotected and purified by the method used in preparation of compound **A24**, to afford **A32**, the compound of Example 50.

Preparation of Example 51



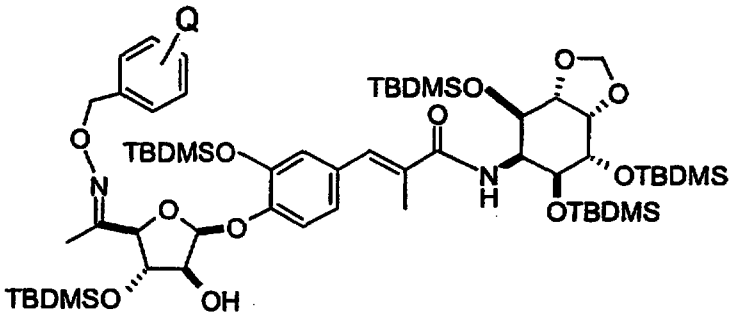
A33

To a solution of **A26** (1 eq.) in tetrahydrofuran (~0.2 M) was added hydrochloric acid (0.2 N)(1000 eq.). After 1 hour the reaction was diluted with ethyl acetate and washed with saturated sodium bicarbonate solution, pH 7.0 phosphate buffer solution (0.05 M) and dried over magnesium sulfate. After filtration and concentration the crude phenol was purified by silica gel chromatography, eluting with a step gradient of 5% ethyl acetate in hexanes to 33% ethyl acetate in hexanes.

A solution of the above bromoketone (1 eq.) in dimethylformamide (0.1 M) at 4°C was treated with the appropriate 1-(phenyl)-2-thiourea (6 eq.). After completion (1 hour) the reaction was diluted with hexanes and diethyl ether (roughly 1:1), washed with pH 7.0 phosphate buffer solution (0.05 M), saturated sodium chloride and then dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by silica gel chromatography, eluting with a step gradient of 5% ethyl acetate in hexanes to 33% ethyl acetate in hexanes.

Protected aminothiazole was deprotected and purified by the method used in preparation of compound **A24**, to afford **A33**, the compound of Example 51.

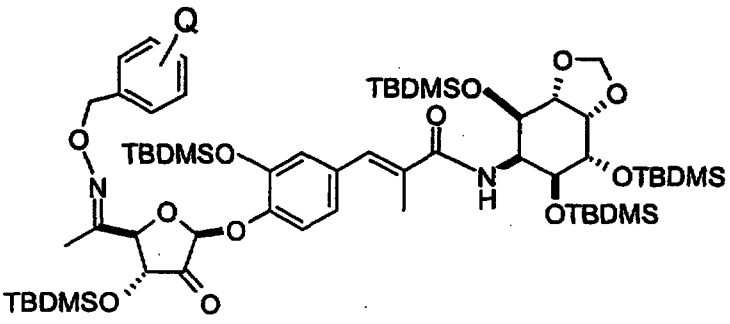
Preparation of Example 52



A34

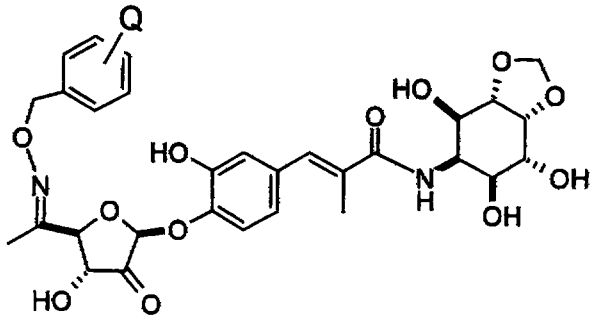
A solution of hygromycin A (1 eq.) in dimethylformamide (0.1 M) was treated with imidazole (10 eq.) and *tert*-butyldimethylsilyl chloride (10 eq) at 35°C for 15 hours. The reaction was poured into water and extracted with ethyl acetate. The combined extracts were dried over magnesium sulfate and concentrated. The product was obtained after chromatography eluting with a step gradient of 5% ethyl acetate in hexanes to of 15% ethyl acetate in hexanes.

The appropriate oxime was introduced using the chemistry described in preparation of the p-fluorophenyl compound **A15**, until tlc showed the reaction was substantially complete, to afford **A34**.



A35

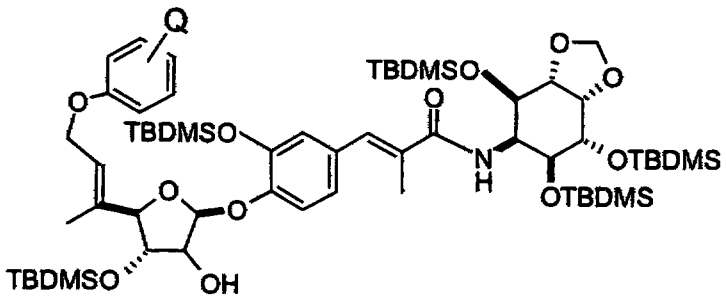
A solution of **A34** (1 eq.) in dichloromethane (0.1 M) was treated with Dess-Martin periodinane (2.6 eq.). After 7 hours the reaction was diluted with dichloromethane and washed with saturated sodium bicarbonate solution and brine. The organic layer was dried with magnesium sulfate, filtered and evaporated to afford **A35**.



A36

Protected ketone, **A35**, was deprotected and purified by the method used in preparation of compound **A24**, to afford **A36**, the compound of Example 52.

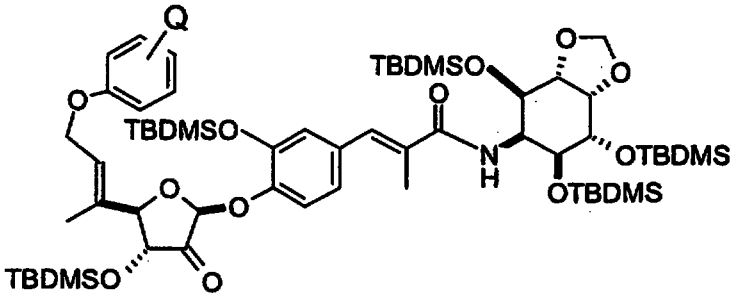
Preparation of Example 53



A37

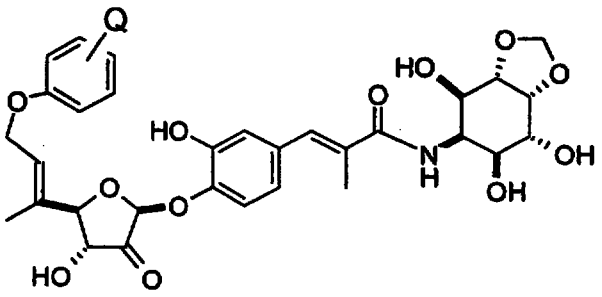
A solution of hygromycin A (1 eq.) in dimethylformamide (0.1 M) was treated with imidazole (10 eq.) and *tert*-butyldimethylsilyl chloride (10 eq) at 35°C for 15 hours. The reaction was poured into water and extracted with ethyl acetate. The combined extracts were dried over magnesium sulfate and concentrated. The product was obtained after chromatography eluting with a step gradient of 5% ethyl acetate in hexanes to of 15% ethyl acetate in hexanes.

The appropriate allyl ether was introduced using the method described for preparation of **A25**, to afford **A37**.



A38

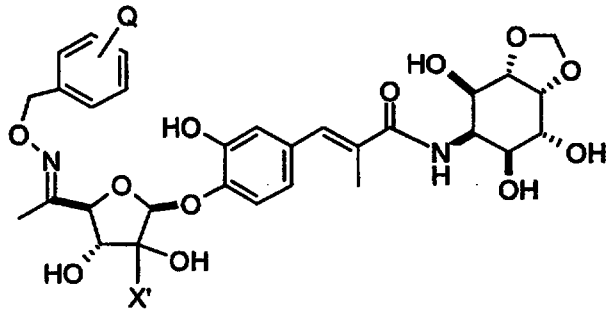
A solution of **A37** (1 eq.) in dichloromethane (0.1 M) was treated with Dess-Martin periodinane (2.6 eq.). After 7 hours the reaction was diluted with dichloromethane and washed with saturated sodium bicarbonate solution and brine. The organic layer was dried with magnesium sulfate, filtered and evaporated to afford **A38**.



A39

Protected ketone, **A38**, was deprotected and purified by the method used in preparation of compound **A24**, to afford **A39**, the compound of Example 53.

Preparation of Examples 54-56



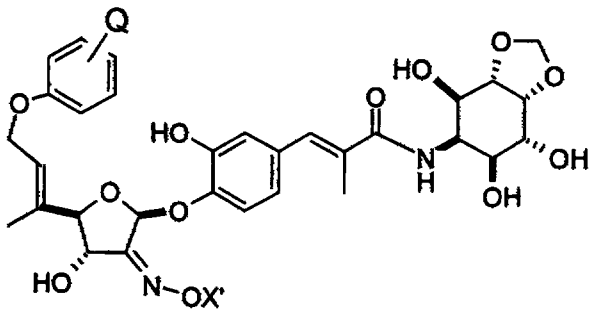
A40

To a solution of **A35** (1 eq.) in tetrahydrofuran (0.05 M) at -15°C was added the appropriate Grignard reagent (3-5 eq.) and the reactions were allowed to slowly warm to room temperature. After 10-20 hours the reactions were diluted with ethyl acetate, washed with pH 7.0 phosphate buffer solution (0.05 M) and saturated sodium chloride and then dried over

magnesium sulfate, filtered, and concentrated. The crude products were purified by silica gel chromatography, eluting with a step gradient of 5% ethyl acetate in hexanes to 20% ethyl acetate in hexanes.

Protected adducts, of undefined stereochemistry at C2", were deprotected and purified by the method used in preparation of compound **A24**, to afford **A40**, the compounds of Examples 54 - 56.

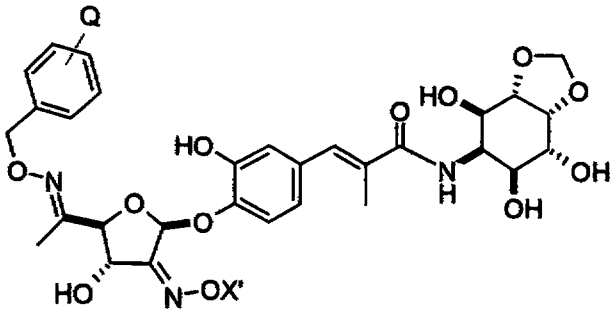
Preparation of Example 57



A41

To a solution of **A39** (1 eq.) in methanol (0.025 M) was added the appropriate hydroxylamine (2.5 eq.) and the reaction warmed to 50°C. After 20-30 hours the reaction was concentrated and was purified by silica gel chromatography, eluting with a step gradient of 5% methanol in dichloromethane to 20% methanol in dichloromethane to afford **A41**, the compound of Example 57.

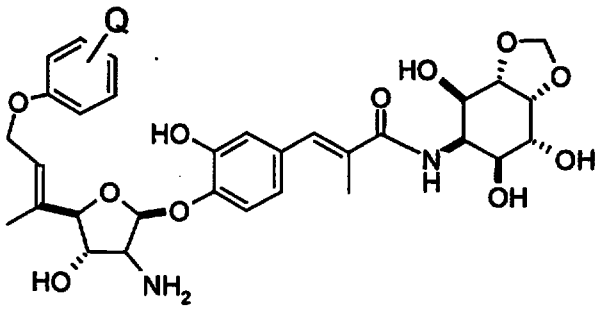
Preparation of Example 58



A42

Compound **A42** was prepared from **A36** using the chemistry described for preparation of **A41**.

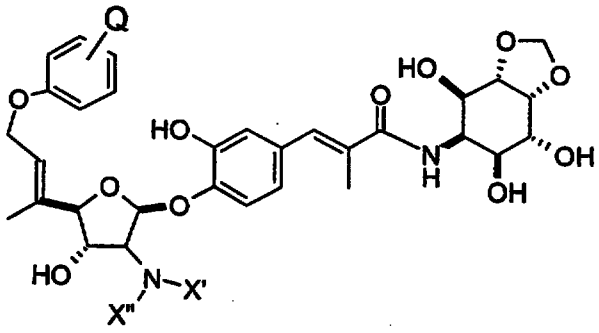
Preparation of Example 59



A43

To a solution of **A41** (where X' = H, 1 eq.) in methanol (0.05 M) was added ammonium acetate (15 eq.) followed by the slow addition of titanium tetrachloride (2.5 eq.). After 10 minutes the reaction was neutralized with sodium bicarbonate, filtered and concentrated. The crude imine was taken up in methanol (0.05 M) and sodium borohydride (5.7 eq.) was added. After 10 minutes the reaction was acidified to pH 2 with hydrochloric acid (1 N). After 5 minutes the reaction was brought to pH 10 with sodium hydroxide (1 M) and concentrated and purified by silica gel chromatography, eluting with a step gradient of 5% methanol in dichloromethane to 20% methanol in dichloromethane to afford **A43** with undefined C2" stereochemistry.

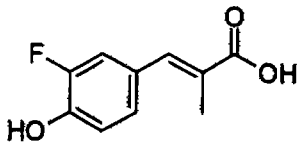
Preparation of Examples 60-61



A44

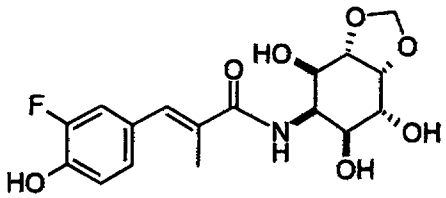
To a solution of **A39** (1 eq.) in methanol (0.03 M) was added the appropriate amine (8-10 eq.) followed by sodium cyanoborohydride (2.5 eq.). After 15-20 hours the reactions were acidified to pH 2 with hydrochloric acid (1 N). After 5 minutes the reactions were neutralized with sodium hydroxide (1 M) and concentrated and purified by silica gel chromatography, eluting with a step gradient of 2.5% methanol in dichloromethane to 10% methanol in dichloromethane to afford the compounds represented by **A44** with undefined C2" stereochemistry.

Preparation of Examples 62, and 67-80



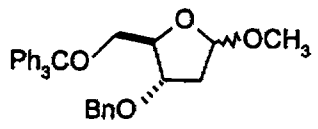
A45

4-Methoxy-3-fluorobenzaldehyde in dichloromethane (0.16 M) was treated with BBr_3 (1.5 eq.) and stirred for 9-10 hours. The reaction was quenched by the addition of excess methanol and the mixture was warmed to 70°C for 30 minutes. After concentration the residue was dissolved in Et_2O, washed with water and brine, and concentrated. The resultant hydroxyaldehyde in dichloromethane (0.13 M) was treated with carbethoxy-ethylidenetriphenylphosphorane (1.2 eq) for about 15 hours. The reaction mixture was concentrated and chromatographed using a gradient from hexane to 15% ethyl acetate in hexane. This ester was hydrolyzed using LiOH (7 eq.) in a solution of 3THF:2methanol:1water (0.05 M) at a temperature of 60°C overnight. The reaction was quenched by the addition of 1N HCl and the product **A45** was isolated by extraction with ethyl acetate.

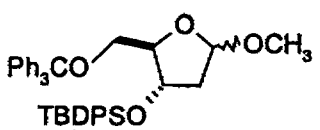


A46

Compound of the formula **A46** was prepared by heating a mixture of inositol **2** (Scheme 1, Fragment A) (2 eq) and compound **A45** with EEDQ (1.2 eq.) in DMF (0.1 M) to 60°C for 3 hours and stirring at room temperature overnight. Concentration of the reaction mixture and chromatography using a step gradient of 5% to 20% methanol in chloroform provided **A46**.



A47

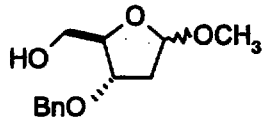


A47.1

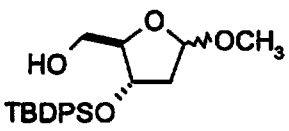
Compound **A47** was prepared by treatment of the corresponding secondary alcohol (1 eq.) (*J. Org. Chem.*, **1995**, *60*, 202) with benzyl bromide (1.5 eq.) and sodium hydride (2 eq.) in THF (0.1 M) and stirring overnight. The reaction was quenched with water and extracted with ethyl

acetate. Concentration and chromatography with 5-10% ethyl acetate in hexanes provided **A47**.

Alternatively, compound **A47.1** was prepared by treatment of the same secondary alcohol with tert-butyldiphenyl silyl chloride (1.2 eq.) and imidazole (1.5 eq) in DMF at room temperature for 12-18 h. The reaction was quenched with water and extracted with methylene chloride. The combined organics were washed with brine and dried over $MgSO_4$ and concentrated. The residue was purified using a step gradient of 5% to 10% ethyl acetate in hexanes to provide **A47.1**.

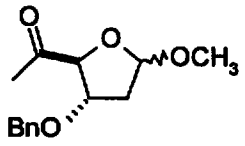


A48

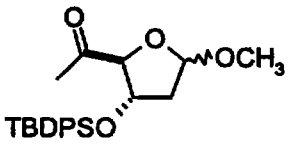


A48.1

Compound **A48** was prepared by treatment of **A47** in methanol (0.1 M) with 0.5% HCl in methanol for 1.5 hours. The reaction mixture was quenched with Ag_2CO_3, filtered and concentrated. Product **A48** was obtained after chromatography with a step gradient of 15% to 35% ethyl acetate in hexanes. Compound **A48.1** was prepared in an analogous manner and isolated upon chromatography using a step gradient of 5% to 20% ethyl acetate in hexanes.

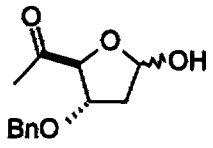


A49

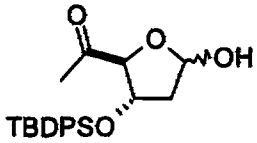


A49.1

Compound **A49** was prepared by adding **A48** to a mixture of oxalyl chloride (2 eq.) and DMSO (4 eq.) in methylene chloride at –78°C (substrate concentration, 0.05 M). After 1 hour, triethylamine (8 eq.) was added and the reaction warmed to room temperature. Water was added and the crude aldehyde was obtained by extraction with ether and concentration. A solution of this aldehyde in THF (0.05 M) was treated with methyl magnesium bromide (2 eq.) at –78°C. The reaction was quenched with sodium bicarbonate, extracted with Et_2O and concentrated to provide a mixture of alcohols. Compound **A49** was prepared by adding that mixture of alcohols to a mixture of oxalyl chloride (2 eq.) and DMSO (4 eq.) in methylene chloride at –78°C (substrate concentration, 0.05 M). After 1 hour, triethylamine (8 eq.) was added and the reaction warmed to room temperature. Water was added and **A49** was obtained by extraction with ether, concentration and chromatography using a step gradient of 10% to 20% ethyl acetate in hexanes. Compound **A49.1** was prepared in an analogous fashion and obtained upon chromatography using a step gradient of 10% to 20% ethyl acetate in hexanes.

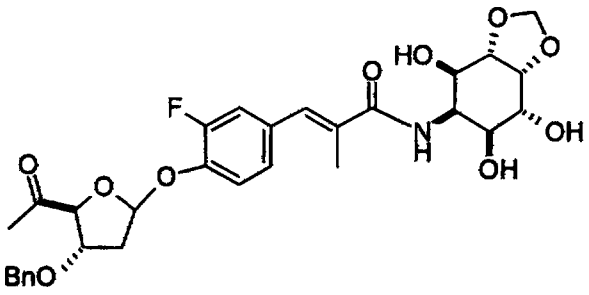


A50



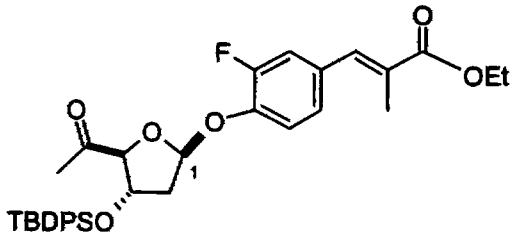
A50.1

Compound **A50** was prepared by treatment of **A49** with a solution of 80% trifluoroacetic acid (0.1 M) for 2 hours. The reaction was poured into a saturated solution of sodium bicarbonate and extracted with ethyl acetate. Upon concentration the crude residue was chromatographed with 20% ethyl acetate in hexanes to provide **A50**. Compound **A50.1** was prepared in an analogous fashion and obtained upon chromatography using a step gradient of 10% to 25% ethyl acetate in hexanes.



A51

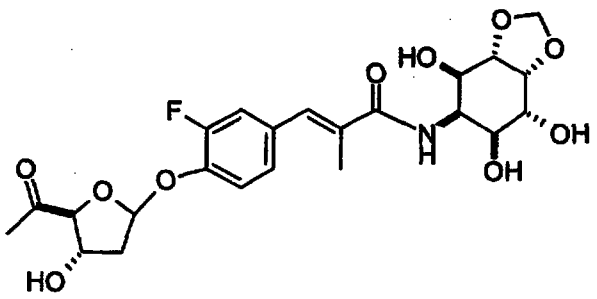
Compound **A51** was prepared by treatment of a mixture of **A50** (1 eq.) and **A46** (1.5 eq.) with diethylazodicarboxylate (1.6 eq.) and PPh_3 (1.6 eq.) in THF (0.15 M in substrate **A50**) and stirring overnight. The reaction mixture was concentrated and chromatographed on silica gel using a step gradient of 3% to 10% methanol in chloroform to provide **A51** as a mixture of diastereomers.



A51.1

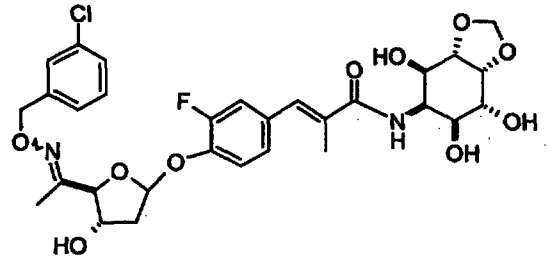
Compound **A51.1** was prepared in an analogous fashion and obtainedwith the advantage each C-1 isomer could be isolated upon chromatography using a step gradient of 5% to 20%

ethyl acetate in hexanes. Each of the isomers was converted separately to the examples shown below but only the β isomer will be described.

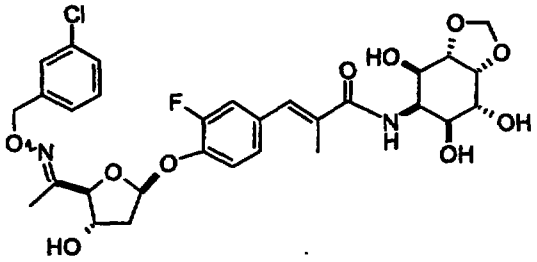


A52

Compound **A52** was prepared by treatment of a solution of **A51** in ethanol (0.05 M) with 10% Pd/C (1:1 wt:wt) and 1,4-cyclohexadiene (20 eq.) and stirring overnight. The reaction mixture was filtered through celite, concentrated and chromatographed on silica gel using a step gradient of 5% to 15% methanol in chloroform to provide **A52**.

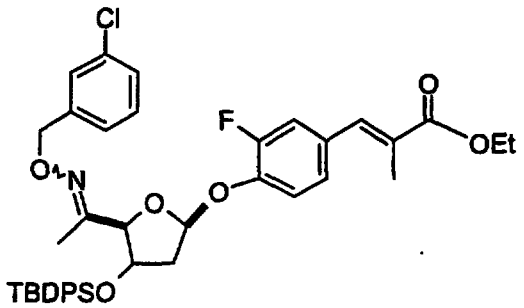


A53



A53.1

Compound **A53** was prepared by treatment of a solution of **A52** in methanol (0.1 M) with N-(3-chlorophenylmethyl)hydroxylamine (1.5 eq.) overnight. The reaction was concentrated and the residue was chromatographed on silica gel using a step gradient of 5% to 10% methanol in chloroform to provide **A53**, the compound of Example 62.

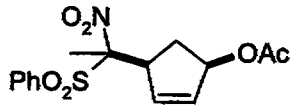


A53.2

Compound **A53.2** was prepared by treatment of a solution of **A51.1** in methanol (0.1 M) with N-(3-chlorophenylmethyl)hydroxylamine (1.5 eq.) overnight. The reaction was concentrated and the residue was chromatographed on silica gel using a step gradient of 5% to 10% methanol in chloroform to provide **A53.2**.

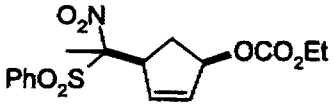
Compound **A53.1** was also prepared by treatment of **A53.2** with 1 M sodium hydroxide (3 eq.) in a THF/methanol (1/1) solution at room temperature for 12-18 h whereupon the reaction was heated to 50 °C for 3h. The reaction was quenched with dilute acetic acid and extracted with ethyl acetate. The combined organics were dried over $MgSO_4$ and concentrated to provide the crude acid, which was used without further purification. A solution of the acid , DCC (2 eq.) N-hydroxybenztriazole (2 eq) and 4-dimethyaminopyridine (1.5 eq.) was treated with inositol **2** (Scheme 1, Fragment A) (4 eq) at room temperature for 12-18 h. The reaction was concentrated and the residue was chromatographed using a step gradient of 3% to 10% methanol in chloroform to provide **A53.1**, the compound of example 66.

Preparation of Example 77:



A54

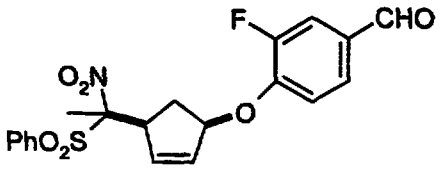
Compound **A54** was prepared by treatment of the corresponding ethyl carbonate (Deardorff *et. al. J. Org. Chem.* **1996**, 61, 3616) with $Pd(dba)_3$ (0.05 eq.), triphenylphosphine (0.2 eq.), Et_3N (1.2 eq.), 1,1-phenylsulphonyl-nitroethane (1.2 eq.) in THF at °C for 2 h. The reaction was concentrated and the residue was chromatographed using a step gradient of 5% to 20% ethyl acetate in hexanes to provide **A54**



A55

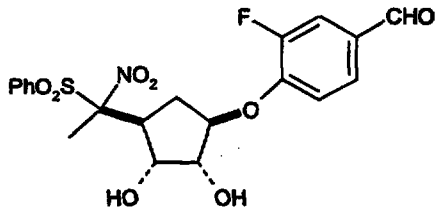
Compound **A55** was prepared by treatment of **A54** with K_2CO_3 (1.2 eq.) in THF, water, methanol (2:1:1) at room temperature for 2 h. The reaction was diluted with water and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The resulting material was used without purification and treated with ethylchloroformate (1.3 eq) and pyridine (8 eq.) in methylene chloride at rt for 12-18 h. The reaction was quenched with a saturated solution of ammonium chloride, acidified with 1 N HCl and extracted with methylene chloride. The combined organics were dried over $MgSO_4$ and

concentrated. The residue was chromatographed using a step gradient of 10% to 30% ethyl acetate in hexanes to provide **A55**.



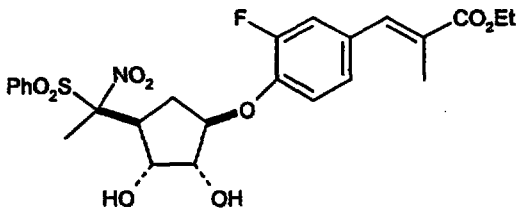
A56

Compound **A56** was prepared by treatment of **A55** with $Pd(dba)_3$ (0.05 eq.), triisopropyl phosphite (0.25 eq.), $CeCO_3$ (2.2 eq.), 3-fluoro-4-hydroxy benzaldehyde (2 eq.) in THF at rt for 3 h. Water and ether were added and the reaction was extracted with ether and the organic extracts dried over $MgSO_4$. The reaction was concentrated and the residue was chromatographed using a step gradient of 10% to 30% ethyl acetate in hexanes to provide **A56.**



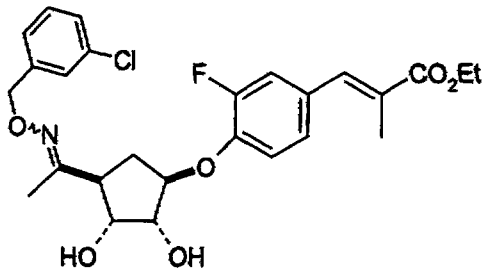
A57

Compound **A57** was prepared by treatment of **A56** with osmium tetroxide (0.05 eq.) N-methylmorpholine-N-oxide (1.5 eq.) in methylene chloride at rt for 12-18 h. The reaction was concentrated and the residue was chromatographed using a step gradient of 20% to 50% ethyl acetate in hexanes to provide **A57**.



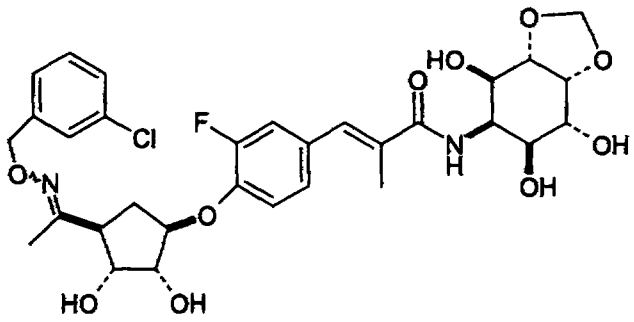
A58

Compound **A58** was prepared by treatment of **A57** with carbethoxy-ethylidenetriphenylphosphorane (1.2 eq.) in methylene chloride at rt for 2 h. The reaction was concentrated and the residue was chromatographed using a step gradient of 10% to 20% ethyl acetate in hexanes to provide **A58.**



A59

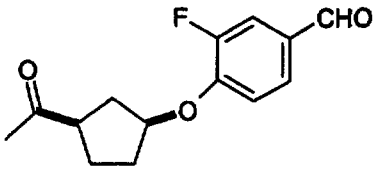
Compound **A59** was prepared by treatment of **A58** with titanium trichloride (10 eq.) in a THF/water (5/13) solution buffered with ammonium acetate (78 eq) at rt for 2 h. The reaction was diluted with water and extracted with ethyl acetate. The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated. The crude residue was chromatographed using a step gradient of 20% to 40 % ethyl acetate in hexanes to provide the desired methyl ketone. The ketone was treated with *O*-3-chlorobenzylhydroxyl amine (1.5 eq.) in methanol at room temperature for 12-18 h. The reaction was concentrated and the residue was chromatographed using a step gradient of 10% to 40 % ethyl acetate in hexanes to provide **A59** as predominantly the *E* isomer.



A60

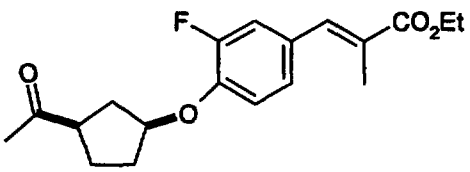
Compound **A60** was prepared by treatment of **A59** with 1 M sodium hydroxide (2 eq.) in a THF/methanol (1/1) solution at room temperature for 12-18 h whereupon the reaction was heated to 50 °C for 3h. The reaction was quenched with dilute acetic acid and extracted with ethyl acetate. The combined organics were dried over $MgSO_4$ and concentrated to provide the crude acid, which was used without further purification. The acid was treated with of inositol **2** (Scheme 1, Fragment A) (3 eq), DCC (2 eq.) N-hydroxybenztriazole (2 eq) and 4-dimethyaminopyridine (1.5 eq.) in DMF at rt for 12-18 h. The reaction was concentrated and the residue was chromatographed using preparative thin layer chromatography (prep TLC) using 15% methanol in chloroform to provide **A60**, the compound of example 77 (MW Calcd ; found).

Preparation of Example 78:



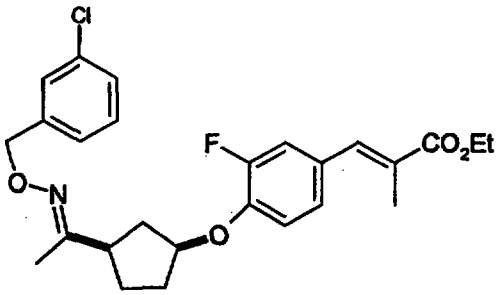
A61

Compound **A61** was prepared by treatment of **A57** with titanium trichloride as with compound **A59.** The resultant unsaturated ketone was treated with Pd on carbon (1mg Pd to 4 mg substrate) in ethanol under an atmosphere of hydrogen at room temperature for 2-5 h. The reaction was filtered, concentrated and the residue chromatographed using a step gradient of 20% to 50% ethyl acetate in hexanes to provide **A61**.



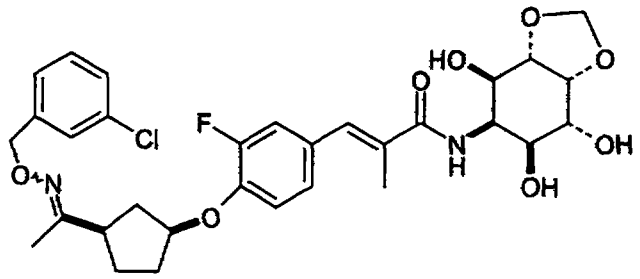
A62

Compound **A62** was prepared by treatment of **A57** with carbethoxy-ethylidenetriphenylphosphorane (1.2 eq.) in methylene chloride at rt for 2 h. The residue was chromatographed using a step gradient of 20% to 50% ethyl acetate in hexanes provided **A62.**



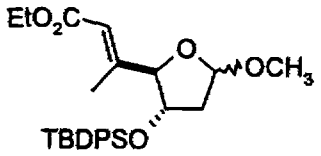
A63

Compound **A63** was prepared by treatment of **A62** with O-3-chlorobenzylhydroxyl amine (1.5 eq.) in methanol at room temperature for 12-18 h. The reaction was concentrated and the residue was chromatographed using a step gradient of 10% to 30 % ethyl acetate in hexanes to provide **A63** as predominantly the *E* isomer.



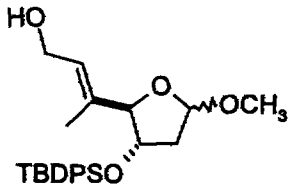
A64

Compound **A64** was prepared the same methods used to prepare **A60** from **A59**. The final product was purified by preparative thin layer chromatography (prep TLC) using 15% methanol in chloroform to provide **A64**, the compound of example 78 (MW Calcd ; found).



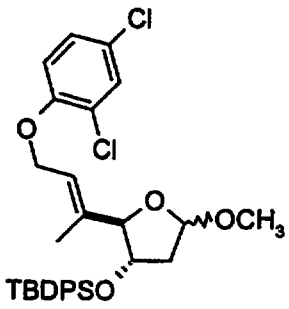
A65

Compound **A65** was prepared by treating compound **A49.1** with (carbethoxymethylene)-triphenylphosphorane (2eq.) in DMF at 50 °C for 12-18 h. The reaction mixture was diluted with 1:1 ether:hexanes and quenched with pH 7 buffer. The aqueous layer was extracted with 1:1 ether:hexanes and the combined organics were washed with water, brine, dried over $MgSO_4$ and concentrated. The crude residue was chromatographed using a step gradient of 3% to 12% ethyl acetate in hexanes to provide **A65**.



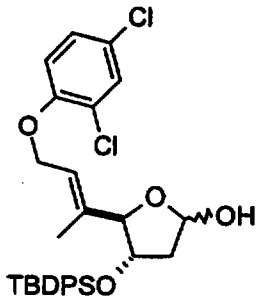
A66

Compound **A66** was prepared by treating compound **A65** with diisobutylaluminum hydride (5eq.) in methylene chloride at -78°C for 30 min. The reaction was quenched at -78°C with a saturated solution of Rochelle's salt (sodium potassium tartrate) and the reaction was allowed to warm to rt. A saturated solution of ammonium chloride was added and the reaction stirred for 1 h. The mixture was extracted with ethyl acetate and the combined organics were washed with brine, dried over $MgSO_4$ and concentrated. The crude residue, **A66**, was used without further purification.



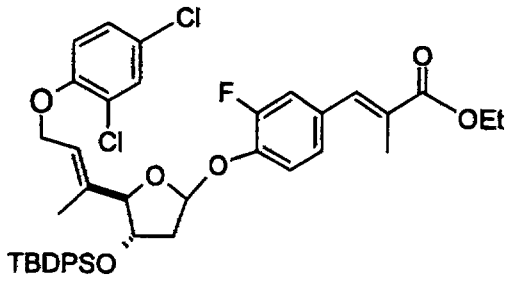
A67

Compound **A67** was prepared by a dropwise addition of a THF solution of diethylazodicarboxylate (2.5 eq.) to a solution of compound **66**, 2.4-diclorophenol (3 eq) (use extreme caution when handling this compound, Hogue, C. *Chemical and Engineering News* **2000**, *18*, p.49) and triphenylphosphine (2.5 eq.) in THF at rt. The reaction was stirred for 1 h and concentrated. The crude residue was chromatographed using a step gradient of 3% to 10% ethyl acetate in hexanes to provide **A67**.



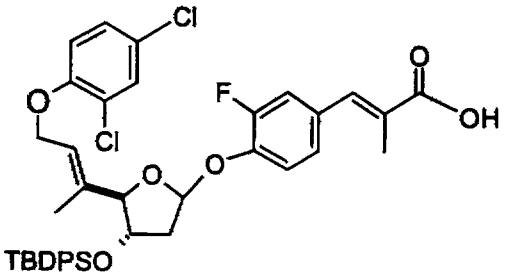
A68

Compound **A68** was prepared treating compound **67** with 80% trifluoroacetic acid in THF at rt for 1.5 h. The reaction was quenched by addition of saturated sodium bicarbonate and extracted into ethyl acetate. The organics were washed with brine , dried over $MgSO_4$ and concentrated. The crude residue was chromatographed using a step gradient of 5% to 20% ethyl acetate in hexanes to provide **A68**.



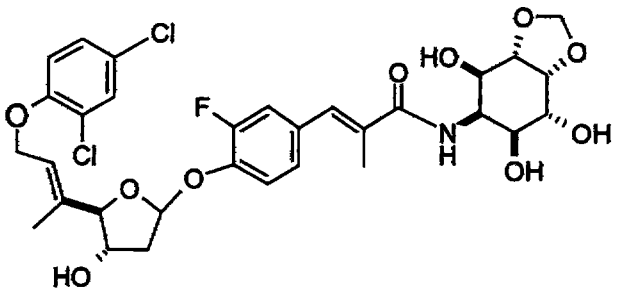
A69

Compound **A69** was prepared from compound **A68** using the methods described for the conversion of **A50.1** to **A51.1**. Compound **A69** was obtained after chromatography using a step gradient of 20% to 30% ethyl acetate in hexanes.



A70

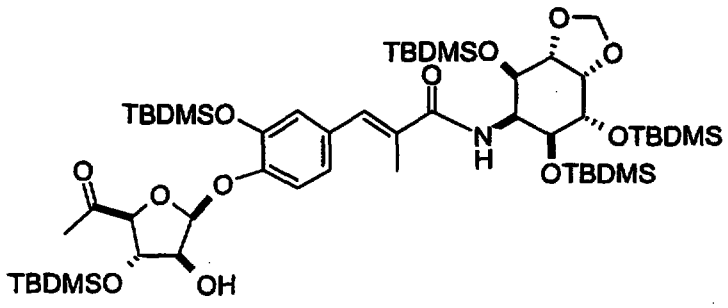
Compound **A70** was prepared by treating compound **A69** with 1 M sodium hydroxide (2 eq.) in a THF/methanol (1/1) solution at 50 °C for 12-18 h. The reaction was quenched with dilute acetic acid (pH ~4) and extracted with ethyl acetate. The combined organics were washed with brine, dried over $MgSO_4$ and concentrated. The crude acid was chromatographed using a step gradient of 40% to 66% ethyl acetate in hexanes to provide **A70**.



A71

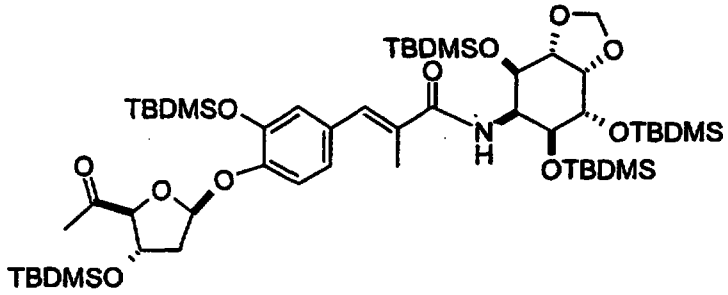
The acid **A70** was treated with of inositol **2** (Scheme 1, Fragment A) (3 eq), DCC (2 eq.) N-hydroxybenztriazole (2 eq) and 4-dimethyaminopyridine (1.5 eq.) in DMF at rt for 12-18 h. The reaction was concentrated and the residue was chromatographed using a step gradient of 3% to 5% methanol in chloroform to provide the desired amide. The silyl group was removed using the method described for the preparation of compound **A14**. Compound **A71** was obtained after chromatography using prep TLC using 10% methanol in chloroform.

Preparation of example 63:



A71

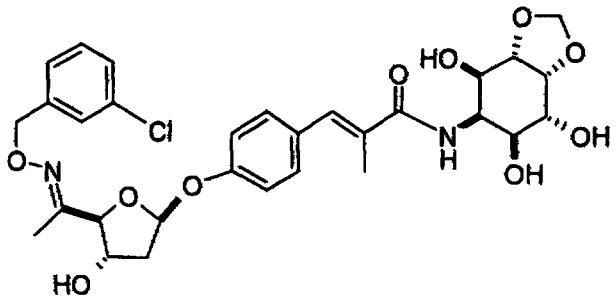
Compound **A71** was prepared when a solution of hygromycin A (1 eq.) in DMF (0.1 M) was treated with imidazole (10 eq) and tert-butyldimethylsilyl chloride (10 eq) at 35 °C for 14-16 h. The reaction was poured into water and extracted with ethyl acetate. The combined extracts were dried over $MgSO_4$ and concentrated. The product was obtained after chromatography using a step gradient of 5% to 15% ethyl acetate in hexanes to provide **A71**.



A72

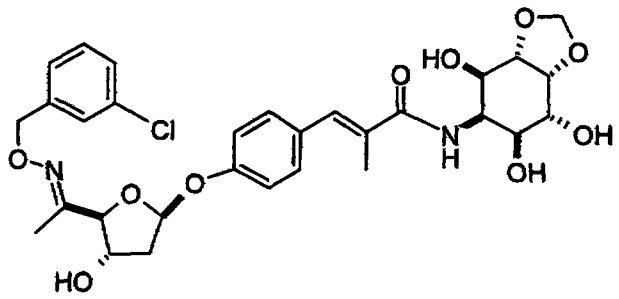
Compound **A72** was prepared when a solution of the compound **A71** (1 eq.) in methylene chloride was treated with phenylthionochloroformate (3 eq.), pyridine (5 eq) and dimethylaminopyridine (0.05 eq.) at rt for 2-3 days. At the end of this time the reaction was diluted with methylene chloride, washed with 0.5 N HCl, saturated sodium bicarbonate and then Brine. The organics were dried over $MgSO_4$ and concentrated. The desired 2"-thionocarbonate was obtained after chromatography using a step gradient of 5% to 10% ethyl acetate in hexanes.

A solution of the above 2"-thionocarbonate (1 eq.) in toluene (0.1 M) was treated with AIBN (1 eq.) and tri-n-butyltinhydride (3 eq.) at 90 °C for 2h. The reaction was concentrated and chromatographed using a step gradient of 5% to 10% ethyl acetate in hexanes. to provide the desired 2"-deoxy compound **A72**.



A73

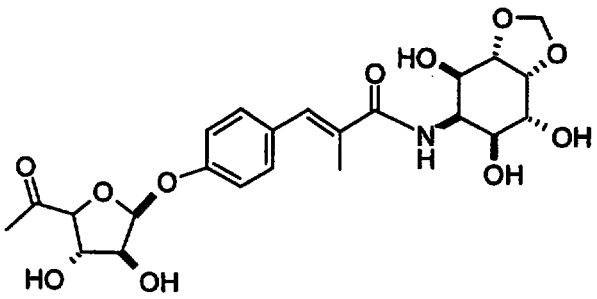
A solution of the compound **A72** (1 eq.) in methanol (0.1 M) was treated with the 3-chlorobenzyl hydroxylamine (1 eq.) at 60 °C for 30 min to 1h. The reaction mixture was concentrated and the desired oxime was obtained after chromatography using a step gradient of 5% to 10% ethyl acetate in hexanes. The silyl protecting groups were removed by the method used to convert **A18** to **A19**, thus providing **A73**.



A74

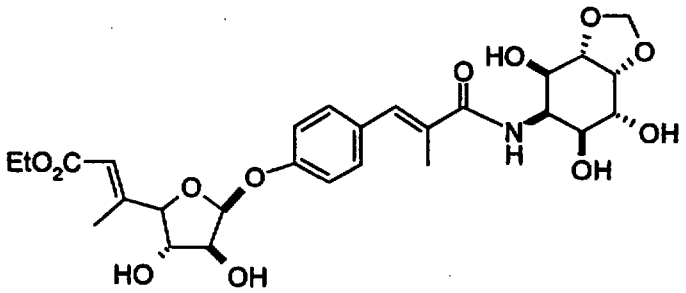
The compound of formula **A74** was prepared by treatment of **A73** with N-phenyl-bis(trifluoromethanesulphonamide) (1.8 eq.) and triethylamine (2 eq.) in DMF at room temperature for 2 h. The reaction mixture was poured into brine and extracted with ethyl acetate. The combined organics were dried over $MgSO_4$ and concentrated. The crude residue was chromatographed using a step gradient of 5% to 15% methanol in chloroform. A solution of the resultant phenyl triflate, tris(dibenzylidineacetone)dipalladium(0)-chloroform adduct (0.04 eq.), 1,1'-bis(diphenylphosphino)ferrocene (0.08 eq.) and triethylamine (7.5 eq.) in DMF was treated with formic acid (5 eq.) and warmed to 60 °C for 5 h. The reaction mixture was poured into brine and extracted with ethyl acetate. The combined organics were dried over $MgSO_4$ and concentrated. The crude residue was chromatographed using a step gradient of 5% to 15% methanol in chloroform. The desired compound **A74** (example 63) was further purified using reverse phase chromatography (C18) using a step gradient of 10% to 50% acetonitrile in water.

Preparation of examples 64-66:



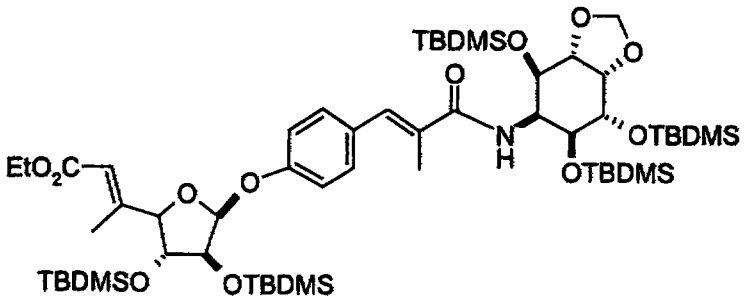
A75

The compound of formula **A75** was prepared by treatment of hygromycin A with N-phenyl-bis(trifluoromethanesulphonamide) (1.8 eq.) and triethylamine (2 eq.) in DMF at room temperature for 2 h. The solvent was removed *en vacuo* and the crude residue was chromatographed using a step gradient of 3% to 15% methanol in chloroform. A solution of the resultant phenyl triflate, tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (0.04 eq.), 1,1'-bis(diphenylphosphino)ferrocene (0.08 eq.) and triethylamine (7.5 eq.) in DMF was treated with formic acid (5 eq.) and warmed to 60 °C for 5 h. The solvent was removed *en vacuo* and the crude residue was chromatographed using a step gradient of 3% to 15% methanol in chloroform to provide the desired compound **A75**.



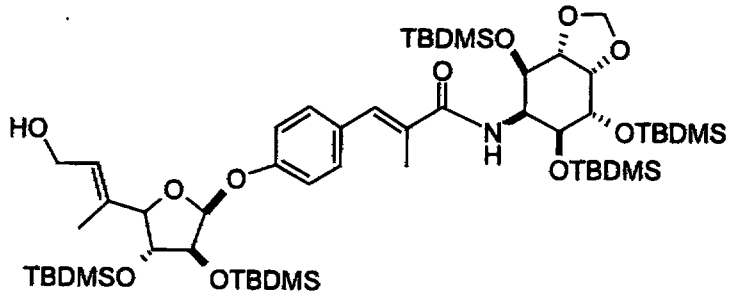
A76

Compound **A76** was prepared by treating compound **A75** with (carbethoxymethylene)-triphenylphosphorane (2eq.) in DMF at 70 °C for 12-18 h. The solvent was removed *en vacuo* and the crude residue was chromatographed using a step gradient of 5% to 10% methanol in chloroform to provide the desired compound **A76**.



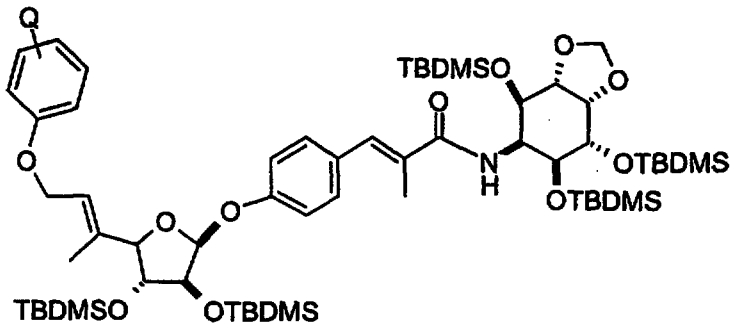
A77

Compound **A77** was prepared when a solution of **A76** (1 eq.) in DMF was treated with imidazole (15 eq) and tert-butyldimethylsilyl chloride (15 eq) at 70 °C for 12-18 h. The reaction was poured into water and extracted with ethyl acetate/hexanes (1/1), washed with water and brine. The combined extracts were dried over $MgSO_4$ and concentrated. The product was obtained after chromatography using a step gradient of 3% to 20% ethyl acetate in hexanes to provide **A77**.



A78

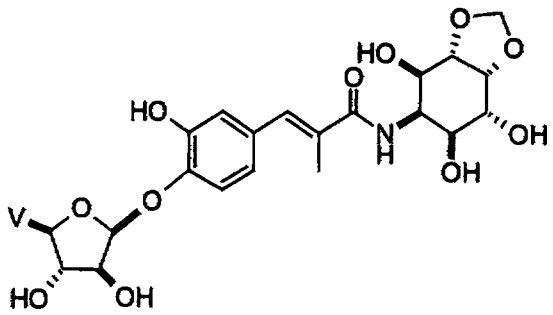
Compound **A78** was prepared by treating compound **A77** with diisobutylaluminum hydride (6eq.) in methylene chloride at -78 °C for 30 min. The reaction was quenched at -78 °C with a saturated solution of Rochelle's salt (sodium potassium tartrate) and the reaction was allowed to warm to rt. The mixture was extracted with chloroform and the combined organics were washed with brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed using a step gradient of 3% to 20% ethyl acetate in hexanes to provide **A78**.

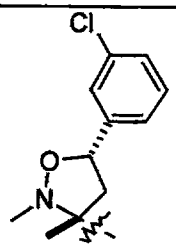
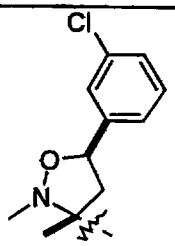
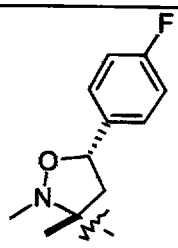
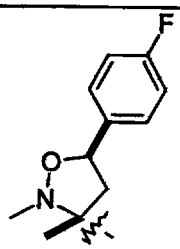


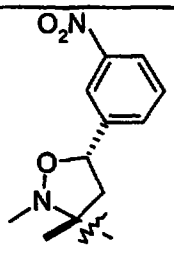
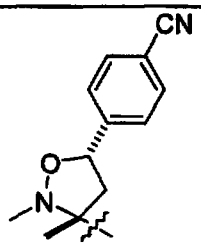
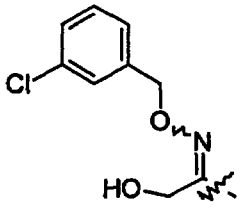
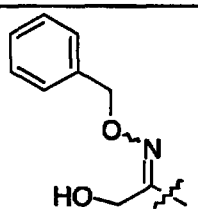
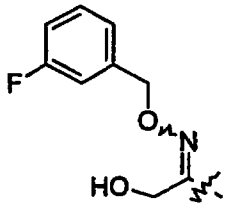
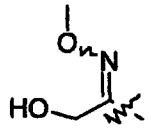
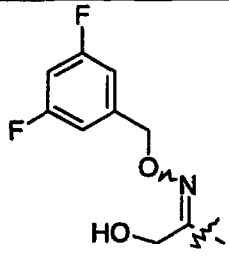
A79

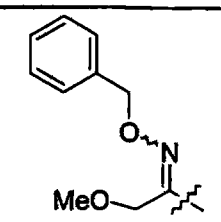
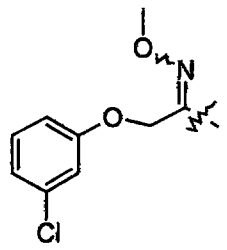
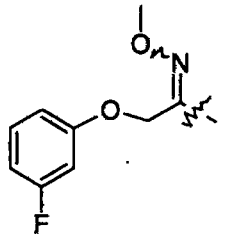
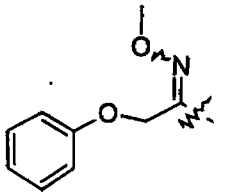
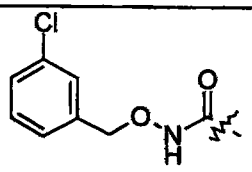
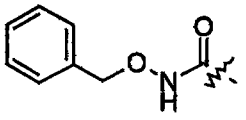
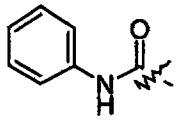
Compounds of the formula **A79** were prepared by a dropwise addition of diethylazodicarboxylate (2.5 eq.) to a solution of compound **A78**, the appropriate phenol (5 eq) and triphenylphosphine (5 eq.) in toluene at 0 °C. The reaction was stirred for 10 min and was diluted with ethyl acetate. The mixture was extracted with brine and the combined organics dried over $MgSO_4$ and concentrated. The crude residue was chromatographed using a step gradient of 3% to 20% ethyl acetate in hexanes to provide **A67**. The silyl protecting groups were removed by the method used to convert **A18** to **A19**, thus providing **A79**.

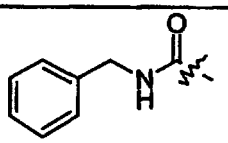
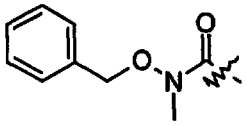
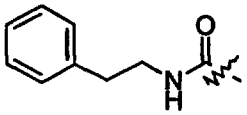
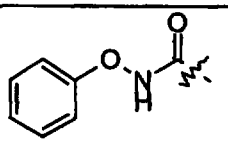
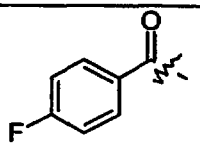
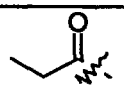
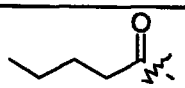
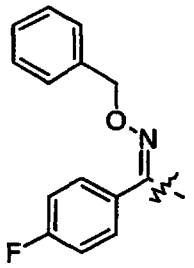
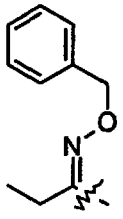
Table 1

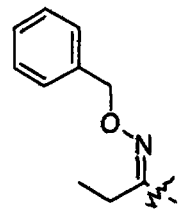
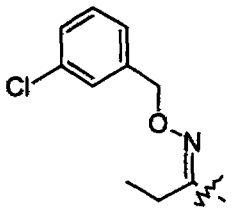
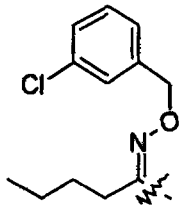
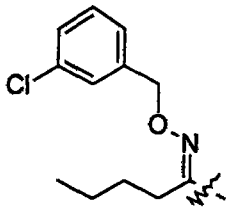
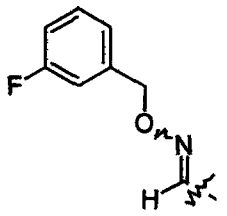
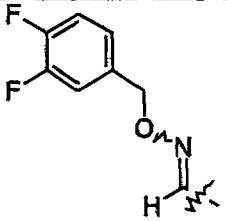
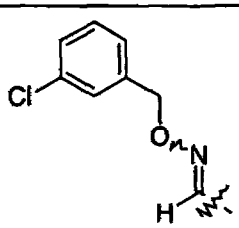


Example	V	Stereo	Mol. Wt.	Mass Spec.
1			679.1	679.3
2			679.1	679.0
3			662.7	662.9
4			662.7	663.1

5			689.7	690.2
6			669.7	669.9
7		E,Z mix	667.1	666.7
8		E,Z mix	632.6	633.6
9		E,Z mix	650.6	651.1
10		E,Z mix	556.5	557.0
11		E,Z mix	668.6	669.0

12		E,Z mix	646.7	647.4
13		E,Z mix	667.1	667.3
14		E,Z mix	650.6	651.3
15		E,Z mix	632.6	633.3
16			653.0	653.0
17			618.6	619.6
18			588.6	589.2

19			602.6	602.9
20			632.6	633.2
21			616.6	617.4
22			604.6	605.2
23			591.5	592.3
24			525.5	526.6
25			553.6	554.5
26		E	696.7	697.9
27		Z	630.7	631.5

28		E	630.7	631.5
29		E	665.1	665.4
30		Z	693.2	693.5
31		E	693.2	693.5
32		E,Z mix	620.6	621.6
33		E,Z mix	638.6	638.7
34		E,Z mix	637.0	636.7

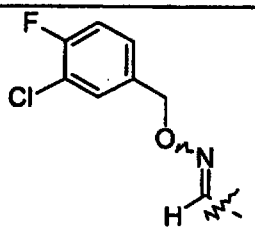
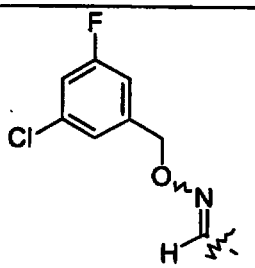
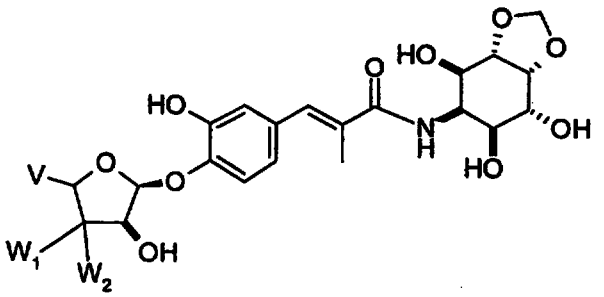
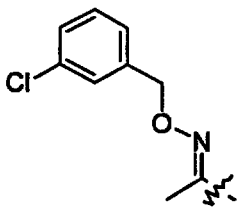
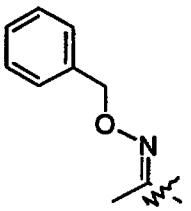
35		E,Z mix	655.0	655.4
36		E,Z mix	655.0	654.5

Table 2



Example	V	Stereo	W¹, W²	Mol. Wt.	Mass Spec.
37		E oxime		665.1	665.2
38		E,Z mix; both isomers at C-4"		600.6	601.3

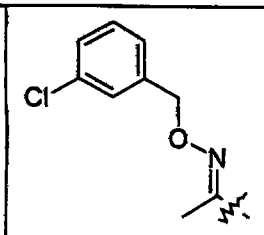
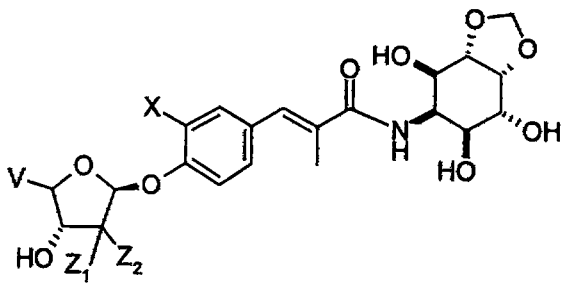
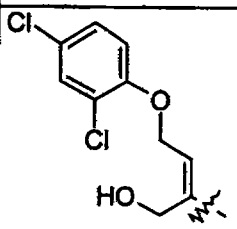
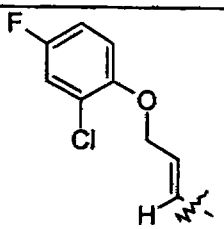
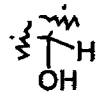
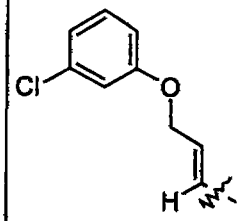
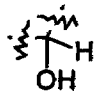
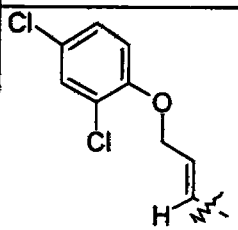
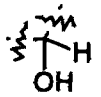
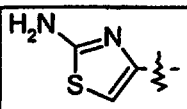
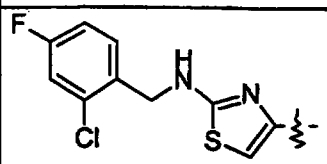
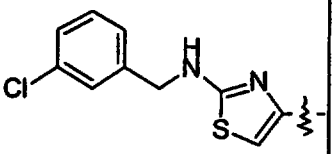
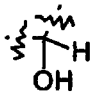
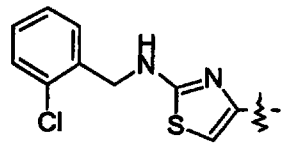
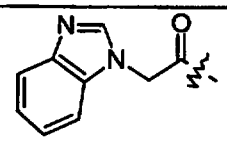
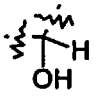
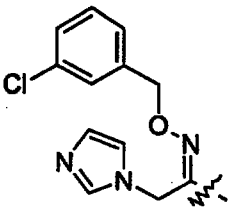
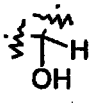
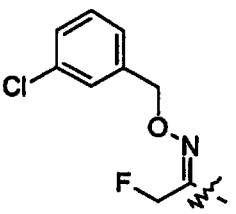
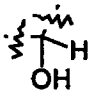
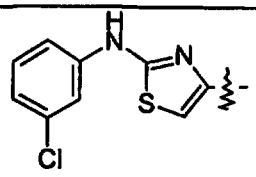
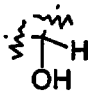
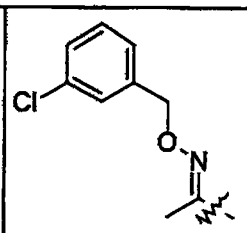
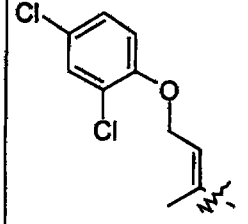
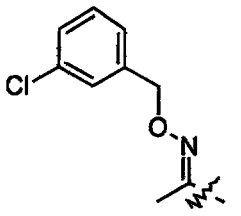
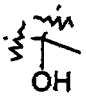
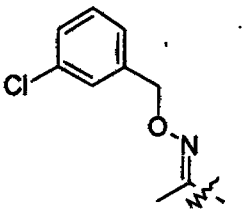
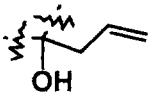
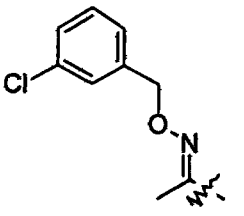
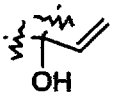
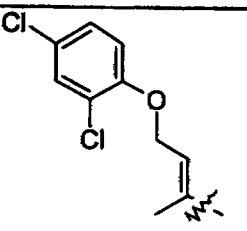
39		E,Z mix; both isomers at C-4"		635.1	635.3

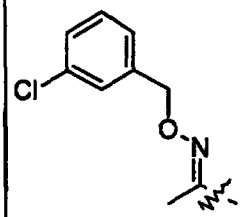
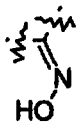
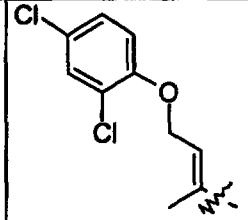
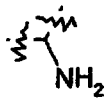
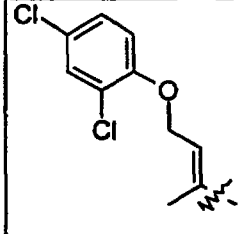
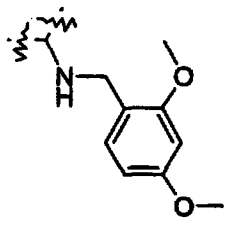
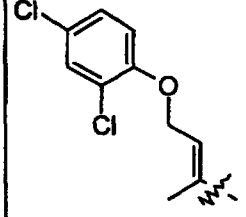
Table 3



Example	V	Stereo	Z^1, Z^2	X	Mol Wt	Mass spec
40		E		OH	700.5	700.3
41		E		OH	654.1	654.4
42		E		OH	636.1	636.1
43		E		OH	670.5	671.8

44				OH	567.6	568.0
45				OH	710.1	710.0
46				OH	692.1	692.1
47				OH	692.1	692.0
48				OH	627.6	628.1
49		E		OH	717.1	717.1
50		Z		OH	669.1	669.3
51				OH	678.1	678.4

52		E		OH	649.1	649.7
53		E		OH	682.5	682.7
54		E		OH	665.1	665.3
55		E		OH	691.1	691.5
56		E		OH	677.1	677.3
57		E		OH	697.5	697.5

58		E		OH	664.1	664.3
59		E		OH	683.5	684.4
60		E		OH	833.7	883.7
61		E		OH	697.6	697.6

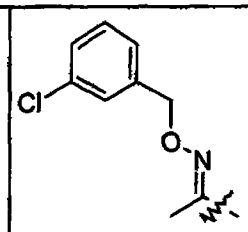
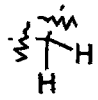
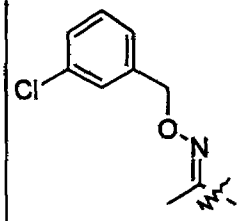
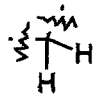
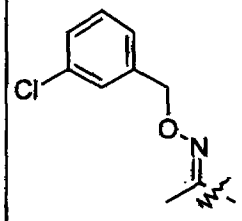
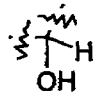
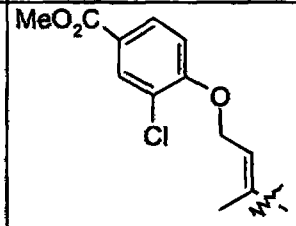
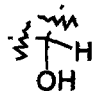
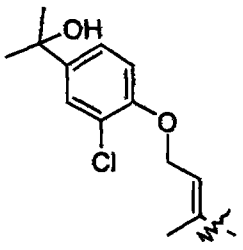
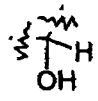
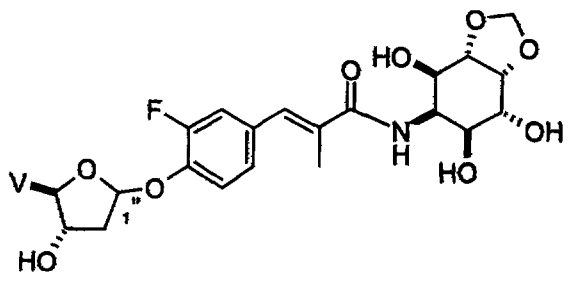
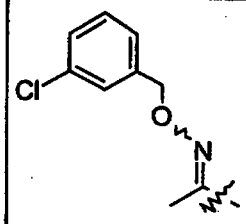
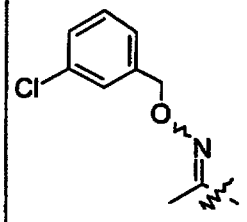
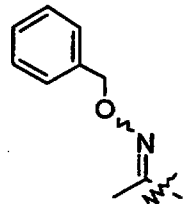
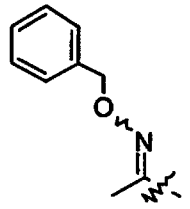
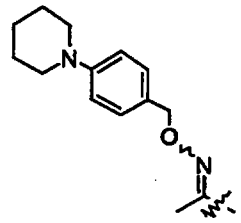
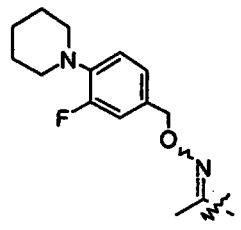
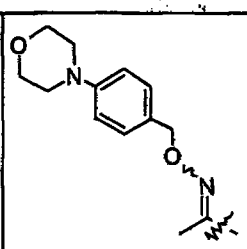
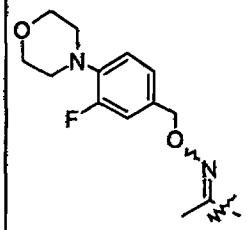
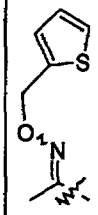
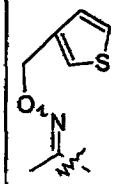
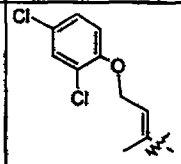
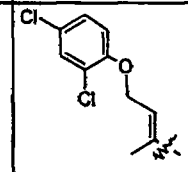
62		E, Z mix		F	637.1	637.4
63		E		H	618.2	619.0
64		E, Z mix		H	633.2	635.2
65		E		H	691.2	692.1
66		E		H	691.2	690.3 (M-1)

Table 4



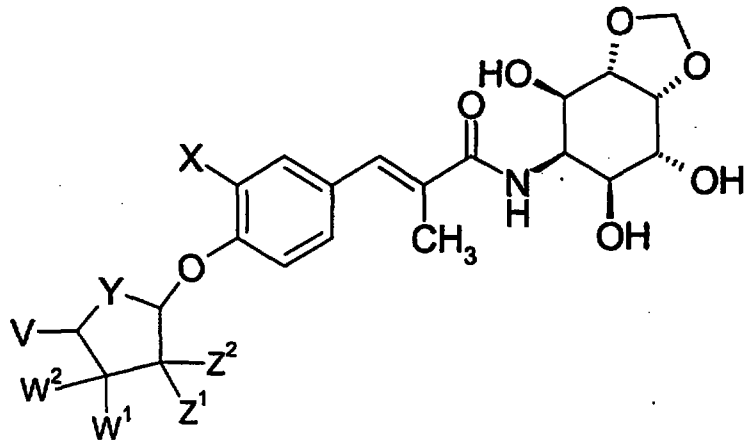
5

Example	V	Stereo	C-1" stereochemistry	Mol Wt	Mass spec
67		E,Z mix	β	637.1	637.4
68		E,Z mix	α	637.1	637.1
69		E,Z mix	α	602.2	602.7
70		E,Z mix	β	602.2	603.0
71		E,Z mix	β	685.3	685.6
72		E,Z mix	β	703.3	704.2

73		E,Z mix	β	687.3	688.1
74		E,Z mix	β	705.3	706.2
75		E,Z mix	β	608.2	609.1
76		E,Z mix	β	608.2	609.1
Examples 77 and 78 are in the text					
79		E	β	669.2	669.7
80		E	α	669.2	669.5

CLAIMS

1. A compound of the formula



1

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

X is H, F, OH, or NH_2;

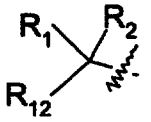
Y is O or CH_2;

Z^1 is R^3 and Z^2 is OR^{13}; or Z^1 is H and Z^2 is R^3, $-NR^3R^4$, $-NR^3C(O)R^4$, or F;

or Z^1 and Z^2 are taken together to form =O or $=NOR^3$;

W^1 is R^3 and W^2 is OR^{13}; or W^1 is H and W^2 is R^3, $-NR^3R^4$, $-NR^3C(O)R^4$, or F;

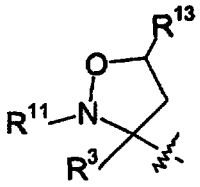
or W^1 and W^2 are taken together to form =O or $=NOR^3$;



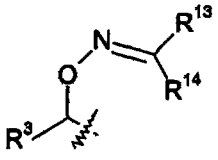
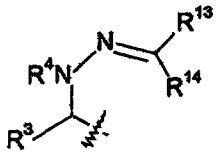
V is a group having the following structure

or V is $R^3OC(O)$-, $R^3R^4NC(O)$- or $R^3O(R^4)NC(O)$-, in which groups R^3 and R^4 optionally can be taken together to form a 4 to 10 membered heterocyclic group which may be optionally substituted by 1 to 3 R^6 groups;

or V is a group having the following structure:





or V is a group of the structure  or , where both E and Z isomers are included;

or V is a carbon-linked 4 to 10 membered heterocyclic group, which may be optionally substituted by 1 to 3 R^6 groups;

R^1 is H and R^2 is $-NR^3R^4$, $-NR^4C(O)R^3$, $-OC(O)NR^3R^4$ or $-OR^3$;

or R^1 and R^2 are taken together to form O, $=N-OR^3$, or $=C(R^5)X^1-X^2-R^8$, wherein:

X^1 is $-CR^9R^{10}-$, and X^2 is selected from $-CR^9R^{10}-$, $-S(O)_n-$ wherein n is an integer from 0 to 2, $-NR^9-$, and O; where X^2 is $-NR^9-$, then R^8 and R^9 may be taken together to form a 5 to 12 membered heterocyclic group, which is optionally substituted by 1 to 3 R^6 groups; or X^1 and X^2 independently or together represent a bond with the proviso that if X^1 is a bond than X^2 is either a bond or $-CR^9R^{10}-$;

each R^3 is independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(CR^9R^{10})_t(C_3$-C_{10} cycloalkyl), $-(CR^9R^{10})_t(C_6$-C_{10} aryl), and $-(CR^9R^{10})_t$(4 to 10 membered heterocyclic), wherein each t is independently an integer from 0 to 5, said alkyl, alkenyl and alkynyl groups optionally contain 1 or 2 hetero moieties selected from O, $-S(O)_j-$ wherein j is an integer from 0 to 2, and $-N(R^9)-$ with the proviso that two O atoms, two S atoms, or an O and S atom are not attached directly to each other, and the proviso that an O atom, a S atom or a N atom are not attached directly to a triple bond or non-aromatic double bond; said cycloalkyl, aryl and heterocyclic R^3 groups are optionally fused to a benzene ring, a C_5-C_8 cycloalkyl group, or a 4 to 10 membered heterocyclic group; the $-(CR^9R^{10})_t-$ moieties of the foregoing R^3 groups optionally include a carbon-carbon double or triple bond where t is an integer between 2 and 5; and the foregoing R^3 groups, except H but including any optional fused rings referred to above, are optionally substituted by 1 to 5 R^6 groups, and with the proviso that R^3 must be attached through a carbon atom unless R^3 is H;

each R^4 is independently H or C_1-C_{10} alkyl;

R^5 is H or C_1-C_6 alkyl, wherein the foregoing R^5 alkyl group is optionally substituted by 1 or 2 R^6 groups

each R^6 is independently selected from C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, oxo, halo, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-OR^7$, $-C(O)R^7$, $-C(O)OR^7$, $-NR^9C(O)OR^{11}$, $-OC(O)R^7$, $-NR^9SO_2R^{11}$, $-SO_2NR^7R^9$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, $-NR^7R^9$, $-S(O)_j(CR^9R^{10})_m(C_6$-$C_{10}$ aryl), $-S(O)_j(C_1$-C_6 alkyl), wherein j is an integer from 0 to 2, $-(CR^9R^{10})_m(C_6$-C_{10} aryl), $-O(CR^9R^{10})_m(C_6$-C_{10} aryl), $-NR^9(CR^9R^{10})_m(C_6$-C_{10} aryl), and $-(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an

integer from 0 to 4; said alkyl, alkenyl and alkynyl groups optionally contain 1 or 2 hetero moieties selected from O, $-S(O)_j-$ wherein j is an integer from 0 to 2, and $-N(R^7)-$ with the proviso that two O atoms, two S atoms, or an O and S atom are not attached directly to each other, and the proviso that an O atom, a S atom or a N atom are not attached directly to a triple bond or a non-aromatic double bond; said cycloalkyl, aryl and heterocyclic R^6 groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 cycloalkyl group, or a 4 to 10 membered heterocyclic group; and said alkyl, cycloalkyl, aryl and heterocyclic R^6 groups are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-NR^9SO_2R^{11}$, $-SO_2NR^7R^9$, $-C(O)R^7$, $-C(O)OR^7$, $-OC(O)R^7$, $-NR^9C(O)OR^{11}$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, $-NR^7R^9$, $-OR^7$, C_1-C_{10} alkyl, $-(CR^9R^{10})_m(C_6$-C_{10} aryl), and $-(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 4;

each R^7 is independently selected from H, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, $-(CR^9R^{10})_m(C_6$-C_{10} aryl), and $-(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer from 0 to 4; said alkyl group optionally includes 1 or 2 hetero moieties selected from O, $-S(O)_j-$ wherein j is an integer ranging from 0 to 2, and $-N(R^9)-$ with the proviso that two O atoms, two S atoms, or an O and S atom are not attached directly to each other; said cycloalkyl, aryl and heterocyclic R^7 groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 cycloalkyl group, or a 4 to 10 membered heterocyclic group; and the foregoing R^7 substituents, except H, are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-C(O)R^9$, $-C(O)OR^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)NR^9R^{10}$, $-NR^9R^{10}$, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy, and with the proviso that R^7 must be attached through a carbon atom unless R^7 is H;

each R^8 is independently selected from R^3, $-C(O)R^3$, or $-C(O)NR^9R^3$, wherein R^3 is as defined above;

each R^9 and R^{10} is independently H or C_1-C_6 alkyl; and,

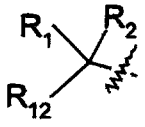
R^{11} is selected from the substituents provided in the definition of R^7 except H.

R^{12} is selected from the substituents provided in the definition of R^3, except that R^{12} cannot be methyl if (a) X is OH, Y is O, W^1 is H, W^2 is α-OH, Z^1 is H, Z^2 is β-OH; or (b) if X is OH, Y is O, W^1 is H, W^2 is α-OH, Z^1 and Z^2 are both H; and with the proviso that R^{12} must be attached through a carbon atom unless R^{12} is H;

R^{13} is defined as described for R^3; and,

R^{14} is H or C_1 –C_{10} alkyl, except that R^{14} cannot be H when R^{13} is H.



2. A compound according to claim 1 wherein V equals 

and R^1 and R^2 are taken together as =O or =NOR^3, and the configuration of the 1" center is that of hygromycin A.

3. A compound according to claim 2 wherein:

Z^1 is R^3 and Z^2 is OR^{13}; or Z^1 is H and Z^2 is R^3, -NR^3R^4, -$NR^3C(O)R^4$, or F; and W^1 is R^3 and W^2 is OR^{13}; or W^1 is H and W^2 is R^3, -NR^3R^4, -$NR^3C(O)R^4$, or F; wherein each R^3 and R^{13} are independently selected from H, C_1-C_4 alkyl, -$(CR^9R^{10})_t$(C_3-C_{10} cycloalkyl), -$(CR^9R^{10})_t$(C_6-C_{10} aryl), and -$(CR^9R^{10})_t$(4 to 10 membered heterocyclic), wherein each t is independently an integer from 0 to 3, said alkyl group optionally contains 1 hetero moiety selected from O, -$S(O)_j$- wherein j is an integer from 0 to 2, and -$N(R^9)$-, and the foregoing R^3 and R^{13} groups, except H, are optionally substituted by 1 to 5 R^6 groups, and with the proviso that R^3 and R^{13} must be attached through a carbon atom unless it is H; each R^4 is independently H or C_1-C_4 alkyl; each R^6 is independently selected from C_1-C_4 alkyl, oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, -OR^7, -$C(O)R^7$, -$NR^9C(O)OR^{11}$, -$NR^9C(O)R^7$, -$C(O)NR^7R^9$, -NR^7R^9; wherein R^7 and R^9 are H, C_1-C_4 alkyl; R^{11} is C_1-C_4 alkyl;

R^1 and R^2 are taken together as =O or =NOR^3, wherein each R^3 is independently selected from C_1-C_4 alkyl, C_3-C_8 alkenyl, -$(CR^9R^{10})_t$(C_6-C_{10} aryl), and -$(CR^9R^{10})_t$(4 to 10 membered heterocyclic), wherein each t is independently an integer ranging from 0 to 3, said alkyl and alkenyl groups optionally contain 1 or 2 hetero moieties selected from O, -$S(O)_j$- wherein j is an integer ranging from 0 to 2 and -$N(R^9)$-, with the proviso that two O atoms, two S atoms, or an O and S atom are not attached directly to each other, and the proviso that an O atom, a S atom or a N atom are not attached directly to a non-aromatic double bond; said aryl and heterocyclic R^3 groups are optionally fused to a benzene ring, a C_5-C_8 cycloalkyl group, or a 4 to 10 membered heterocyclic group; and the foregoing R^3 groups, including any optional fused rings referred to above, are optionally substituted by 1 to 5 R^6 groups, and with the proviso that R^3 must be attached through a carbon atom; R^{12} is C_1-C_4 alkyl, and said alkyl group is optionally substituted by 1 to 3 R^6 groups, except that R^{12} cannot be methyl if (a) X is OH, Y is O, W^1 is H, W^2 is α-OH, Z^1 is H, Z^2 is β-OH, or if (b) X is OH, Y is O, W^1 is H, W^2 is α-OH, Z^1 is H, Z^2 is H; each R^6 is independently selected from C_1-C_4 alkyl, oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, -OR^7, -$C(O)R^7$, -$NR^9C(O)OR^{11}$, -$NR^9SO_2R^{11}$, -$SO_2NR^7R^9$, -$NR^9C(O)R^7$, -$C(O)NR^7R^9$, -NR^7R^9, -$S(O)_j(CR^9R^{10})_m$(C_6-C_{10} aryl), -$S(O)_j$(C_1-C_6 alkyl), wherein j is an integer ranging from 0 to 2, -$(CR^9R^{10})_m$(C_6-C_{10} aryl), -$O(CR^9R^{10})_m$(C_6-C_{10} aryl), -$NR^9(CR^9R^{10})_m$(C_6-C_{10} aryl), and -$(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer from 0 to 2; and said alkyl, cycloalkyl, aryl and

heterocyclic R^6 groups are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-NR^9SO_2R^{11}$, $-C(O)R^7$, $-NR^9C(O)OR^{11}$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, $-NR^7R^9$, $-OR^7$, C_1-C_4 alkyl, $-(CR^9R^{10})_m(C_6$-C_{10} aryl), and $-(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer from 0 to 2; R^7 is independently selected from H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, $-(CR^9R^{10})_m(C_6$-C_{10} aryl), and $-(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer from 0 to 2; said alkyl group optionally includes 1 hetero moiety selected from O, $-S(O)_j$- wherein j is an integer from 0 to 2, and $-N(R^9)$-; said cycloalkyl, aryl and heterocyclic R^7 groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 cycloalkyl group, or a 4 to 10 membered heterocyclic group; and the foregoing R^7 substituents, except H, are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-C(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)NR^9R^{10}$, $-NR^9R^{10}$, hydroxy, C_1-C_4 alkyl, and C_1-C_4 alkoxy, and with the proviso that R^7 must be attached through a carbon atom unless R^7 is H; R^9 and R^{10} are independently H, C_1-C_4 alkyl; R^{11} is selected from R^7 except H.

4. A compound according to claim 3 wherein:

X is F, H or OH;

Y is O;

W^1 is R^3, W^2 is OR^{13}; or W^1 is H, W^2 is R^3 or F; Z^1 is R^3, Z^2 is OR^{13}; or Z^1 is H, Z^2 is R^3 or F; wherein R^3 and R^{13} are independently H, C_1-C_4 alkyl, and said alkyl groups are optionally substituted by 1 to 3 R^6 groups; wherein each R^6 is independently oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-OR^7$, $-C(O)R^7$, $-NR^9C(O)OR^{11}$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, or $-NR^7R^9$; wherein R^7 and R^9 are H or C_1-C_4 alkyl; R^{11} is C_1-C_4 alkyl;

R^1 and R^2 are taken together as $=NOR^3$, R^3 is $-(CR^9R^{10})_t(C_6$-C_{10} aryl), and $-(CR^9R^{10})_t$(4 to 10 membered heterocyclic), wherein each t is independently an integer from 0 to 3; the foregoing R^3 groups are optionally substituted by 1 to 5 R^6 groups, and with the proviso that R^3 must be attached through a carbon atom; R^{12} is C_1-C_4 alkyl, and said alkyl group is optionally substituted by 1 to 3 R^6 groups, except that R^{12} cannot be methyl if (a) X is OH, Y is O, W^1 is H, W^2 is α-OH, Z^1 is H, Z^2 is β-OH, or if (b) X is OH, Y is O, W^1 is H, W^2 is α-OH, Z^1 is H, Z^2 is H; wherein R^6 is C_1-C_4 alkyl, oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-OR^7$, $-C(O)R^7$, $-NR^9C(O)OR^{11}$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, $-NR^7R^9$, $-(CR^9R^{10})_m(C_6$-C_{10} aryl), $-O(CR^9R^{10})_m(C_6$-C_{10} aryl), $-NR^9(CR^9R^{10})_m(C_6$-C_{10} aryl), and $-(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer from 0 to 2; said alkyl, aryl and heterocyclic R^6 groups are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, trifluoromethyl, difluoromethoxy,

trifluoromethoxy, $-NR^9SO_2R^{11}$, $-C(O)R^7$, $-NR^9C(O)OR^{11}$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, $-NR^7R^9$, $-OR^7$, and C_1-C_4 alkyl;

R^7 is independently selected from H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, $-(CR^9R^{10})_m(C_6$-C_{10} aryl), and $-(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 2; the foregoing R^7 substituents, except H, are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-C(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)NR^9R^{10}$, $-NR^9R^{10}$, hydroxy, C_1-C_4 alkyl, and C_1-C_4 alkoxy; each R^9 and R^{10} are independently H or C_1-C_4 alkyl; R^{11} is selected from R^7 except H.

5. A compound according to claim 4 wherein:

Z^1 is H, Z^2 is OH; or Z^1 is methyl, Z^2 is OH; or both Z^1 and Z^2 are H; or Z^1 is H, Z^2 is F;

W^1 is H, W^2 is OH;

R^1 and R^2 are taken together as $=NOR^3$, wherein R^3 is $-(CR^9R^{10})_t(C_6$-C_{10} aryl), and $-(CR^9R^{10})_t$(4 to 10 membered heterocyclic), wherein each t is independently an integer ranging from 0 to 2, and the foregoing R^3 groups are optionally substituted by 1 to 5 R^6 groups; wherein R^6 is C_1-C_4 alkyl, oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-OR^7$, $-C(O)R^7$, $-(CR^9R^{10})_m(C_6$-C_{10} aryl), $-O(CR^9R^{10})_m(C_6$-C_{10} aryl), and $-(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 2; said alkyl, aryl and heterocyclic R^6 groups are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-C(O)R^7$, $-NR^9C(O)OR^{11}$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, $-OR^7$, and C_1-C_4 alkyl;

R^7 is independently selected from H, C_1-C_4 alkyl; the foregoing R^7 substituents, except H, are optionally substituted by 1 to 3 substituents independently selected from trifluoromethyl, $-C(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)NR^9R^{10}$, $-NR^9R^{10}$, hydroxy, and C_1-C_4 alkoxy; R^9 and R^{10} are independently H, C_1-C_4 alkyl; R^{11} is selected from R^7 except H; R^{12} is C_1-C_4 alkyl except that R^{12} cannot be methyl if (a) X is OH, Y is O, W^1 is H, W^2 is α-OH, Z^1 is H, Z^2 is β-OH, or if (b) X is OH, Y is O, W^1 is H, W^2 is α-OH, Z^1 is H, Z^2 is H.

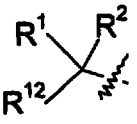
6. A compound according to claim 5 wherein:

R^1 and R^2 are taken together as $=NOR^3$, wherein R^3 is $-(CR^9R^{10})_t$-phenyl, and $-(CR^9R^{10})_t$(5 to 9 membered heterocyclic), where t is 0 or 1, and the foregoing R^3 groups are optionally substituted by 1 to 5 R^6 groups, wherein each R^6 is independently C_1-C_4 alkyl, halo, trifluoromethyl, and $-(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer from 0 to 1; said heterocyclic R^6 groups are optionally substituted by 1 to 5 substituents independently selected from halo, trifluoromethyl, and C_1-C_4 alkyl; each R^9 and R^{10} is independently H or C_1–C_3 alkyl.

7. A compound according to claim 1 wherein:

* C L M S *



V equals 

and R^1 and R^2 are taken together as $=C(R^5)X^1\text{-}X^2\text{-}R^8$ and the configuration of the 1" center is that of hygromycin A.

8. A compound according to claim 7 wherein:

W^1 is R^3, W^2 is OR^{13}; or W^1 is H, W^2 is R^3, NR^3R^4, $NR^3C(O)R^4$, or F; Z^1 is R^3, Z^2 is OR^{13}; or Z^1 is H, Z^2 is R^3, NR^3R^4, $NR^3C(O)R^4$, or F; wherein R^3 and R^{13} are independently selected from H, C_1-C_4 alkyl, $-(CR^9R^{10})_t(C_3\text{-}C_{10}$ cycloalkyl), $-(CR^9R^{10})_t(C_6\text{-}C_{10}$ aryl), and $-(CR^9R^{10})_t$(4 to 10 membered heterocyclic), wherein each t is independently an integer ranging from 0 to 3, said alkyl group optionally contains 1 hetero moiety selected from O, $-S(O)_j$- wherein j is an integer ranging from 0 to 2, and $-N(R^9)$-, and the foregoing R^3 and R^{13} groups, except H, are optionally substituted by 1 to 5 R^6 groups, and with the proviso that R^3 and R^{13} must be attached through a carbon atom unless it is H; each R^4 is independently H or C_1-C_4 alkyl; each R^6 is independently selected from C_1-C_4 alkyl, oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-OR^7$, $-C(O)R^7$, $-NR^9C(O)OR^{11}$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, and $-NR^7R^9$; wherein each R^7 and R^9 is independently H or C_1-C_4 alkyl; R^{11} is C_1-C_4 alkyl;

R^1 and R^2 are taken together as $=C(R^5)X^1\text{-}X^2\text{-}R^8$; wherein X^1 is $-CR^9R^{10}$-, and X^2 is selected from $-CR^9R^{10}$-, $-S(O)_n$- wherein n is 0 to 2, $-NR^9$-, and O; where X^2 is $-NR^9$-, then R^8 and R^9 may be taken together to form a 5 to 12 membered heterocyclic, which is optionally substituted by 1 to 3 R^6 groups; X^1 and X^2 can also independently or together represent a bond with the proviso that if X^1 is a bond than X^2 must be either a bond or $-CR^9R^{10}$-;

and where R^5 is H or C_1-C_6 alkyl, wherein the foregoing R^5 alkyl group is optionally substituted by 1 or 2 R^6 groups:

and where each R^8 is independently selected from R^3, $-C(O)R^3$, or $-C(O)NR^9R^3$, with the additional proviso that an N and O atom, and an N and S atom are not attached directly to each other, wherein each R^3 is independently selected from C_1-C_4 alkyl, C_3-C_8 alkenyl, $-(CR^9R^{10})_t(C_6\text{-}C_{10}$ aryl), and $-(CR^9R^{10})_t$(4 to 10 membered heterocyclic), wherein each t is independently an integer ranging from 0 to 3, said alkyl or alkenyl group optionally contains 1 hetero moiety selected from O, $-S(O)_j$- wherein j is an integer ranging from 0 to 2, and $-N(R^9)$-, with the proviso that an O atom, a S atom or a N atom are not attached directly to a non-aromatic double bond; said aryl and heterocyclic R^3 groups are optionally fused to a benzene ring, a C_5-C_8 cycloalkyl group, or a 4 to 10 membered heterocyclic group; and the foregoing R^3 groups, including any optional fused rings referred to above, are optionally substituted by 1 to 5 R^6 groups, and with the proviso that R^3 must be attached through a carbon atom; R^{12} is C_1-C_4 alkyl, and said alkyl group is optionally substituted by 1 to 3 R^6 groups, except that R^{12}

cannot be methyl if (a) X is OH, Y is O, W^1 is H, W^2 is α-OH, Z^1 is H, Z^2 is β-OH, or if (b) X is OH, Y is O, W^1 is H, W^2 is α-OH, Z^1 is H, Z^2 is H; each R^6 is independently selected from C_1-C_4 alkyl, oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-OR^7$, $-C(O)R^7$, $-NR^9C(O)OR^{11}$, $-NR^9SO_2R^{11}$, $-SO_2NR^7R^9$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, $-NR^7R^9$, $-S(O)_j(CR^9R^{10})_m(C_6$-$C_{10}$ aryl), $-S(O)_j(C_1$-C_6 alkyl), wherein j is an integer ranging from 0 to 2, $-(CR^9R^{10})_m(C_6$-C_{10} aryl), $-O(CR^9R^{10})_m(C_6$-C_{10} aryl), $-NR^9(CR^9R^{10})_m(C_6$-C_{10} aryl), and $-(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 2; and said alkyl, cycloalkyl, aryl and heterocyclic R^6 groups are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-NR^9SO_2R^{11}$, $-C(O)R^7$, $-NR^9C(O)OR^{11}$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, $-NR^7R^9$, $-OR^7$, C_1-C_4 alkyl, $-(CR^9R^{10})_m(C_6$-C_{10} aryl), and $-(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 2; R^7 is independently selected from H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, $-(CR^9R^{10})_m(C_6$-C_{10} aryl), and $-(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 2; said alkyl group optionally includes 1 hetero moiety selected from O, $-S(O)_j$- wherein j is an integer ranging from 0 to 2, and $-N(R^9)$-; said cycloalkyl, aryl and heterocyclic R^7 groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 cycloalkyl group, or a 4 to 10 membered heterocyclic group; and the foregoing R^7 substituents, except H, are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-C(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)NR^9R^{10}$, $-NR^9R^{10}$, hydroxy, C_1-C_4 alkyl, and C_1-C_4 alkoxy, and with the proviso that R^7 must be attached through a carbon atom unless R^7 is H; each R^9 and R^{10} are independently H or C_1-C_4 alkyl; R^{11} is selected from R^7 except H and the configuration of the 1" center is that of hygromycin A.

9. A compound according to claim 8 wherein:

X is F, H or OH;

Y is O;

W^1 is R^3, W^2 is OR^{13}; or W^1 is H, W^2 is R^3, NR^3R^4, or F; Z^1 is R^3, Z^2 is OR^{13}; or Z^1 is H, Z^2 is R^3, NR^3R^4, or F; wherein each R^3 and R^{13} are independently H or C_1-C_4 alkyl, and said alkyl groups are optionally substituted by 1 to 3 R^6 groups; wherein each R^6 is independently oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-OR^7$, $-C(O)R^7$, $-NR^9C(O)OR^{11}$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, and $-NR^7R^9$; wherein each R^7 and R^9 is independently H or C_1-C_4 alkyl; R^{11} is C_1-C_4 alkyl;

R^1 and R^2 are taken together as $=C(R^5)X^1$-X^2-R^8; wherein X^1 is $-CR^9R^{10}$-, and X^2 is selected from $-CR^9R^{10}$-, $-S(O)_n$- wherein n is 0 to 2, $-NR^9$-, and O; where X^2 is $-NR^9$-, then R^8 and R^9 may be taken together to form a 5 to 12 membered heterocyclic, which is optionally

substituted by 1 to 3 R^6 groups; X^1 and X^2 can also independently or together represent a bond with the proviso that if X^1 is a bond than X^2 must be either a bond or $-CR^9R^{10}-$;

and where R^5 is H or C_1-C_6 alkyl, wherein the foregoing R^5 alkyl group is optionally substituted by 1 or 2 R^6 groups:

and where R^8 is R^3 wherein each R^3 is independently $-(CR^9R^{10})_t(C_6$-C_{10} aryl) or $-(CR^9R^{10})_t$(4 to 10 membered heterocyclic), wherein each t is independently an integer ranging from 0 to 3; the foregoing R^3 groups are optionally substituted by 1 to 5 R^6 groups, and with the proviso that R^3 must be attached through a carbon atom; R^{12} is C_1-C_4 alkyl, and said alkyl group is optionally substituted by 1 to 3 R^6 groups, except that R^{12} cannot be methyl if (a) X is OH, Y is O, W^1 is H, W^2 is α-OH, Z^1 is H, Z^2 is β-OH, or if (b) X is OH, Y is O, W^1 is H, W^2 is α-OH, Z^1 is H, Z^2 is H; wherein each R^6 is independently C_1-C_4 alkyl, oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-OR^7$, $-C(O)R^7$, $-NR^9C(O)OR^{11}$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, $-NR^7R^9$, $-(CR^9R^{10})_m(C_6$-C_{10} aryl), $-O(CR^9R^{10})_m(C_6$-C_{10} aryl), $-NR^9(CR^9R^{10})_m(C_6$-C_{10} aryl), and $-(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 2; said alkyl, aryl and heterocyclic R^6 groups are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-NR^9SO_2R^{11}$, $-C(O)R^7$, $-NR^9C(O)OR^{11}$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, $-NR^7R^9$, $-OR^7$, and C_1-C_4 alkyl;

each R^7 is independently selected from H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, $-(CR^9R^{10})_m(C_6$-C_{10} aryl), and $-(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 2; the foregoing R^7 substituents, except H, are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-C(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)NR^9R^{10}$, $-NR^9R^{10}$, hydroxy, C_1-C_4 alkyl, and C_1-C_4 alkoxy; each R^9 and R^{10} are independently H or C_1-C_4 alkyl; R^{11} is selected from R^7 except H.

10. A compound according to claim 9 wherein:

Z^1 is H, Z^2 is OH; or Z^1 is methyl, Z^2 is OH; or Z^1 is H, Z^2 is NH_2; or both Z^1 and Z^2 are H; or Z^1 is H, Z^2 is F;

W^1 is H, W^2 is OH;

R^1 and R^2 are taken together as $=C(R^5)X^1$-X^2-R^8; wherein X^1 is $-CH_2-$, and X^2 is selected from $-S(O)_n-$ wherein n is 0 to 2, $-NR^9-$, and O; where X^2 is $-NR^9-$, then R^8 and R^9 may be taken together to form a 5 to 12 membered heterocyclic, which is optionally substituted by 1 to 3 R^6 groups;

and where R^5 is H or C_1-C_6 alkyl, wherein the foregoing R^5 alkyl group is optionally substituted by 1 or 2 R^6 groups:

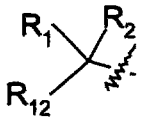
and where R^6 is R^3, wherein R^3 is $-(CH_2)_t(C_6-C_{10}$ aryl) or $-(CH_2)_t$(4 to 10 membered heterocyclic), wherein each t is independently an integer from 0 to 2, and the foregoing R^3 groups are optionally substituted by 1 to 5 R^6 groups; wherein each R^6 is independently C_1-C_4 alkyl, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-OR^7$, $-C(O)R^7$, $-(CH_2)_m(C_6-C_{10}$ aryl), $-O(CH_2)_m(C_6-C_{10}$ aryl), and $-(CH_2)_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer from 0 to 2; said alkyl, aryl and heterocyclic R^6 groups are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-C(O)R^7$, $-NR^9C(O)OR^{11}$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, $-OR^7$, and C_1-C_4 alkyl;

each R^7 is independently selected from H and C_1-C_4 alkyl; the foregoing R^7 substituents, except H, are optionally substituted by 1 to 3 substituents independently selected from oxo, trifluoromethyl, $-C(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)NR^9R^{10}$, $-NR^9R^{10}$, hydroxy, and C_1-C_4 alkoxy; each R^9 and R^{10} are independently H, C_1-C_4 alkyl; R^{11} is selected from R^7 except H; R^{12} is C_1-C_4 alkyl except that R^{12} cannot be methyl if (a) X is OH, Y is O, W^1 is H, W^2 is α-OH, Z^1 is H, Z^2 is β-OH, or if (b) X is OH, Y is O, W^1 is H, W^2 is α-OH, Z^1 is H, Z^2 is H.

11. A compound according to claim 10 wherein:

R^1 and R^2 are taken together as $=C(R^5)X^1-X^2-R^8$; wherein R^5 is H, X^1 is $-CH_2-$, and X^2 is O, and wherein R^8 is R^3, wherein R^3 is phenyl or (5 to 6 membered heterocyclic), and the foregoing R^8 groups are optionally substituted by 1 to 5 R^6 groups, wherein each R^6 is independently selected from C_1-C_4 alkyl, halo, trifluoromethyl, and $-(CH_2)_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 1; said heterocyclic R^6 groups are optionally substituted by 1 to 5 substituents independently selected from halo, trifluoromethyl, and C_1-C_4 alkyl.

12. A compound according to claim 1 wherein:

V equals 

and R^1 is H and R^2 is $-NR^3R^4$, $-NR^4C(O)R^3$, $-OC(O)NR^3R^4$ or $-OR^3$.

X is F, H or OH;

Y is O;

W^1 is R^3, W^2 is OR^{13}; or W^1 is H, W^2 is R^3 or F; Z^1 is R^3, Z^2 is OR^{13}; or Z^1 is H, Z^2 is R^3 or F; wherein each R^3 and R^{13} are independently H or C_1-C_4 alkyl, and said alkyl groups are optionally substituted by 1 to 3 R^6 groups; wherein each R^6 is independently halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-OR^7$, $-C(O)R^7$, $-NR^9C(O)OR^{11}$, $-NR^9C(O)R^7$, $-C(O)NR^7R^9$, or $-NR^7R^9$; wherein each R^7 and R^9 are independently H or C_1-C_4 alkyl; R^{11} is C_1-C_4 alkyl;

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and in the substituent R^2, R^3 is independently selected from H, C_1-C_{10} alkyl, -$(CR^9R^{10})_t$(C_3-C_{10} cycloalkyl), -$(CR^9R^{10})_t$(C_6-C_{10} aryl), and -$(CR^9R^{10})_t$(4 to 10 membered heterocyclic), wherein each t is independently an integer from 0 to 3, said alkyl group optionally contains 1 hetero moiety selected from O, -$S(O)_j$- wherein j is an integer ranging from 0 to 2, and -$N(R^8)$-; said cycloalkyl, aryl and heterocyclic R^3 groups are optionally fused to a benzene ring, a C_5-C_8 cycloalkyl group, or a 4 to 10 membered heterocyclic group; and the foregoing R^3 groups, except H but including any optional fused rings referred to above, are optionally substituted by 1 to 5 R^6 groups, and with the proviso that R^3 must be attached through a carbon atom unless R^3 is H; each R^4 is independently H or C_1-C_6 alkyl; each R^6 is independently C_1-C_4 alkyl, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, -OR^7, -$C(O)R^7$, -$NR^9C(O)OR^{11}$, -$NR^9C(O)R^7$, -$C(O)NR^7R^9$, -NR^7R^9, -$(CR^9R^{10})_m$(C_6-C_{10} aryl), -$O(CR^9R^{10})_m$(C_6-C_{10} aryl), -$NR^9(CR^9R^{10})_m$(C_6-C_{10} aryl), and -$(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 2; said alkyl, aryl and heterocyclic R^6 groups are optionally substituted by 1 to 5 substituents independently selected from halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, -$NR^9SO_2R^{11}$, -$C(O)R^7$, -$NR^9C(O)OR^{11}$, -$NR^9C(O)R^7$, -$C(O)NR^7R^9$, -NR^7R^9, -OR^7, and C_1-C_4 alkyl; each R^7 is independently selected from H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, -$(CR^9R^{10})_m$(C_6-C_{10} aryl), and -$(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 2; the foregoing R^7 substituents, except H, are optionally substituted by 1 to 5 substituents independently selected from halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, -$C(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)NR^9R^{10}$, -NR^9R^{10}, hydroxy, C_1-C_4 alkyl, and C_1-C_4 alkoxy; each R^9 and R^{10} are independently H, C_1-C_4 alkyl; R^{11} is selected from R^7 except H; R^{12} is C_1-C_4 alkyl except that R^{12} cannot be methyl if (a) X is OH, Y is O, W^1 is H, W^2 is α-OH, Z^1 is H, Z^2 is β-OH, or if (b) X is OH, Y is O, W^1 is H, W^2 is α-OH, Z^1 is H, Z^2 is H and the configuration of the 1" center is that of hygromycin A.

13. A compound according to claim 1 wherein:

V is $R^3OC(O)$, $R^3R^4NC(O)$ or $R^3O(R^4)NC(O)$ and the configuration of the 1" center is that of hygromycin A.

X is F, H or OH;

Y is O;

W^1 is R^3, W^2 is OR^{13}; or W^1 is H, W^2 is R^3 or F; Z^1 is R^3, Z^2 is OR^{13}; or Z^1 is H, Z^2 is R^3 or F; wherein each R^3 and R^{13} are independently H or C_1-C_4 alkyl, and said alkyl groups are optionally substituted by 1 to 3 R^6 groups; wherein each R^6 is independently halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, -OR^7, -$C(O)R^7$, -$NR^9C(O)OR^{11}$, -$NR^9C(O)R^7$, -$C(O)NR^7R^9$, or -NR^7R^9; wherein each R^7 and R^9 are independently H or C_1-C_4 alkyl; R^{11} is C_1-C_4 alkyl;

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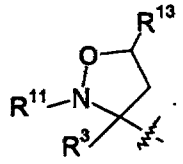
within substituent V, R^3 is independently selected from H, C_1-C_{10} alkyl, -$(CR^9R^{10})_t$(C_3-C_{10} cycloalkyl), -$(CR^9R^{10})_t$(C_6-C_{10} aryl), and -$(CR^9R^{10})_t$(4 to 10 membered heterocyclic), wherein each t is independently an integer ranging from 0 to 3, said alkyl group optionally contains 1 hetero moiety selected from O, -$S(O)_j$- wherein j is an integer ranging from 0 to 2, and -$N(R^9)$-; said cycloalkyl, aryl and heterocyclic R^3 groups are optionally fused to a benzene ring, a C_5-C_8 cycloalkyl group, or a 4 to 10 membered heterocyclic group; and the foregoing R^3 groups, except H but including any optional fused rings referred to above, are optionally substituted by 1 to 5 R^6 groups, and with the proviso that R^3 must be attached through a carbon atom unless R^3 is H; each R^4 is independently H or C_1-C_6 alkyl; each R^6 is independently C_1-C_4 alkyl, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, -OR^7, -$C(O)R^7$, -$NR^9C(O)OR^{11}$, -$NR^9C(O)R^7$, -$C(O)NR^7R^9$, -NR^7R^9, -$(CR^9R^{10})_m$(C_6-C_{10} aryl), -$O(CR^9R^{10})_m$(C_6-C_{10} aryl), -$NR^9(CR^9R^{10})_m$(C_6-C_{10} aryl), and -$(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 2; said alkyl, aryl and heterocyclic R^6 groups are optionally substituted by 1 to 5 substituents independently selected from halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, -$NR^9SO_2R^{11}$, -$C(O)R^7$, -$NR^9C(O)OR^{11}$, -$NR^9C(O)R^7$, -$C(O)NR^7R^9$, -NR^7R^9, -OR^7, C_1-C_4 alkyl; R^7 is independently selected from H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, -$(CR^9R^{10})_m$(C_6-C_{10} aryl), and -$(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 2; the foregoing R^7 substituents, except H, are optionally substituted by 1 to 5 substituents independently selected from halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, -$C(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)NR^9R^{10}$, -NR^9R^{10}, hydroxy, C_1-C_4 alkyl, and C_1-C_4 alkoxy; each R^9 and R^{10} are independently H and C_1-C_4 alkyl; R^{11} is selected from R^7 except H.

14. A compound according to claim 1 wherein:

V is a moiety of the structure  and the configuration of the 1" center is that of hygromycin A.

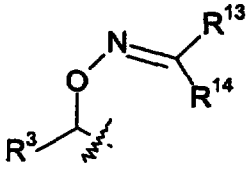
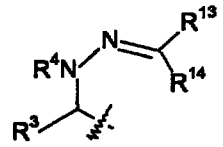
X is F, H or OH;

Y is O;

W^1 is R^3, W^2 is OR^{13}; or W^1 is H, W^2 is R^3 or F; Z^1 is R^3, Z^2 is OR^{13}; or Z^1 is H, Z^2 is R^3 or F; wherein each R^3 and R^{13} are independently H or C_1-C_4 alkyl, and said alkyl groups are optionally substituted by 1 to 3 R^6 groups; wherein each R^6 is independently halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, -OR^7, -$C(O)R^7$, -$NR^9C(O)OR^{11}$, -$NR^9C(O)R^7$, -$C(O)NR^7R^9$, or -NR^7R^9; wherein each R^7 and R^9 is H or C_1-C_4 alkyl; R^{11} is C_1-C_4 alkyl;

within the substituent V, R^3 is C_1-C_6 alkyl; each R^{13} is independently selected from H, C_1-C_{10} alkyl, -$(CR^9R^{10})_t$(C_3-C_{10} cycloalkyl), -$(CR^9R^{10})_t$(C_6-C_{10} aryl), and -$(CR^9R^{10})_t$(4 to 10 membered heterocyclic), wherein each t is independently an integer ranging from 0 to 3, said alkyl group optionally contains 1 hetero moiety selected from O, -$S(O)_j$- wherein j is an integer ranging from 0 to 2, and -$N(R^9)$-; said cycloalkyl, aryl and heterocyclic R^3 groups are optionally fused to a benzene ring, a C_5-C_8 cycloalkyl group, or a 4 to 10 membered heterocyclic group; and the foregoing R^3 groups, except H but including any optional fused rings referred to above, are optionally substituted by 1 to 5 R^6 groups, and with the proviso that R^3 must be attached through a carbon atom unless R^3 is H; each R^6 is independently C_1-C_4 alkyl, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, -OR^7, -$C(O)R^7$, -$NR^9C(O)OR^{11}$, -$NR^9C(O)R^7$, -$C(O)NR^7R^9$, -NR^7R^9, -$(CR^9R^{10})_m$(C_6-C_{10} aryl), -$O(CR^9R^{10})_m$(C_6-C_{10} aryl), -$NR^9(CR^9R^{10})_m$(C_6-C_{10} aryl), and -$(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 2; said alkyl, aryl and heterocyclic R^6 groups are optionally substituted by 1 to 5 substituents independently selected from halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, -$NR^9SO_2R^{11}$, -$C(O)R^7$, -$NR^9C(O)OR^{11}$, -$NR^9C(O)R^7$, -$C(O)NR^7R^9$, -NR^7R^9, -OR^7, and C_1-C_4 alkyl; each R^7 is independently selected from H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, -$(CR^9R^{10})_m$(C_6-C_{10} aryl), and -$(CR^9R^{10})_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 2; the foregoing R^7 substituents, except H, are optionally substituted by 1 to 5 substituents independently selected from halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, -$C(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)NR^9R^{10}$, -NR^9R^{10}, hydroxy, C_1-C_4 alkyl, and C_1-C_4 alkoxy; each R^9 and R^{10} are independently H or C_1-C_4 alkyl; R^{11} is selected from R^7 except H.

15. A compound according to claim 1 wherein:

V is a group of the structure  or  where both E and Z isomers are included or V is a carbon-linked 4 to 10 membered heterocyclic group, which may be optionally substituted by 1 to 3 R^6, and the configuration of the 1" center is that of hygromycin A.

X is F, H or OH;

Y is O;

R^{13} is -$(CR^9R^{10})_t$(C_6-C_{10} aryl) or -$(CR^9R^{10})_t$(4 to 10 membered heterocyclic), wherein each t is independently an integer ranging from 0 to 2, and the foregoing R^3 groups are optionally substituted by 1 to 5 R^6 groups; wherein each R^6 is independently C_1-C_4 alkyl, oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, -OR^7, -$C(O)R^7$, -$(CR^9R^{10})_m$(C_6-C_{10}

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aryl), -O(CR^9R^{10})$_m$(C_6-C_{10} aryl), or -(CR^9R^{10})$_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 2; said alkyl, aryl and heterocyclic R^6 groups are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, -C(O)R^7, -NR^9C(O)OR^{11}, -NR^9C(O)R^7, -C(O)NR^7R^9, -OR^7, and C_1-C_4 alkyl; each R^7 is independently selected from H and C_1-C_4 alkyl; the foregoing R^7 substituents, except H, are optionally substituted by 1 to 3 substituents independently selected from trifluoromethyl, -C(O)R^9, -NR^9C(O)R^{10}, -C(O)NR^9R^{10}, -NR^9R^{10}, hydroxy, and C_1-C_4 alkoxy; each R^9 and R^{10} are independently H or C_1-C_4 alkyl;

each R^4 and R^{14} are independently selected from H and C_1-C_4 alkyl;

R^3 is C_1-C_4 alkyl, and said alkyl group is optionally substituted by 1 to 3 R^6 groups; each R^6 is independently selected from C_1-C_4 alkyl, oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, -OR^7, -C(O)R^7, -NR^9C(O)OR^{11}, -$NR^9SO_2R^{11}$, -$SO_2NR^7R^9$, -NR^9C(O)R^7, -C(O)NR^7R^9, -NR^7R^9, -S(O)$_j$(CR^9R^{10})$_m$(C_6-C_{10} aryl), -S(O)$_j$(C_1-C_6 alkyl), wherein j is an integer ranging from 0 to 2, -(CR^9R^{10})$_m$(C_6-C_{10} aryl), -O(CR^9R^{10})$_m$(C_6-C_{10} aryl), -NR^9(CR^9R^{10})$_m$(C_6-C_{10} aryl), and -(CR^9R^{10})$_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 2; and said alkyl, cycloalkyl, aryl and heterocyclic R^6 groups are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, -$NR^9SO_2R^{11}$, -C(O)R^7, -NR^9C(O)OR^{11}, -NR^9C(O)R^7, -C(O)NR^7R^9, -NR^7R^9, -OR^7, C_1-C_4 alkyl, -(CR^9R^{10})$_m$(C_6-C_{10} aryl), and -(CR^9R^{10})$_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 2; each R^7 is independently selected from H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, -(CR^9R^{10})$_m$(C_6-C_{10} aryl), and -(CR^9R^{10})$_m$(4 to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 2; said alkyl group optionally includes 1 hetero moiety selected from O, -S(O)$_j$- wherein j is an integer ranging from 0 to 2, and -N(R^9)-; said cycloalkyl, aryl and heterocyclic R^7 groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 cycloalkyl group, or a 4 to 10 membered heterocyclic group; and the foregoing R^7 substituents, except H, are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, trifluoromethyl, difluoromethoxy, trifluoromethoxy, -C(O)R^9, -NR^9C(O)R^{10}, -C(O)NR^9R^{10}, -NR^9R^{10}, hydroxy, C_1-C_4 alkyl, and C_1-C_4 alkoxy, and with the proviso that R^7 must be attached through a carbon atom unless R^7 is H; each R^9 and R^{10} are independently H or C_1-C_4 alkyl.

16. A pharmaceutical composition for the treatment of a disorder selected from a bacterial infection, a protozoal infection, and disorders related to bacterial infections or protozoal infections, in a mammal, fish, or bird which comprises a therapeutically effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier.

17. A method of treating a disorder selected from a bacterial infection, a protozoal infection, and disorders related to bacterial infections or protozoal infections, in a mammal, fish, or bird which comprises administering to said mammal, fish or bird a therapeutically effective amount of a compound according to claim 1.

18. A pharmaceutical composition for the treatment of a disorder selected from a bacterial infection, a protozoal infection, and disorders related to bacterial infections or protozoal infections, in a mammal, fish, or bird which comprises a therapeutically effective amount of a compound according to claim 1 in combination with a beta-lactam, quinolone, tetracycline, streptogramin, aminoglycoside, glycopeptide, macrolide or oxazolidinone antibiotic; or in combination with a compound which inhibits bacterial or protozoal efflux or degradation of a compound according to claim 1.

19. A method of treating a disorder selected from a bacterial infection, a protozoal infection, and disorders related to bacterial infections or protozoal infections, in a mammal, fish, or bird which comprises administering to said mammal, fish or bird a therapeutically effective amount of a compound according to claim 1 in combination or co-administered with a beta-lactam, quinolone, tetracycline, streptogramin, aminoglycoside, glycopeptide, macrolide or oxazolidinone antibiotic; or in combination with a compound which inhibits bacterial or protozoal efflux or degradation of a compound according to claim 1.

20. A compound according to claim 1 selected from the group consisting of:

(2S,3S,4S,5S)-3,4-Dihydroxy-5-(2-hydroxy-4-(2-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-ylcarbamoyl)-propenyl)-phenoxy)-tetrahydro-furan-2-carboxylic acid benzyloxy-amide;

3-(4-((2S,3S,5S)-5-(1-((E)-3,4-Difluoro-benzyloxyimino)-ethyl)-3-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide;

3-(4-((2S,3S,4S,5R)-3-Amino-5-(1-((E)-3-chloro-benzyloxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide;

3-(4-((2S,4S,5R)-5-(1-((E)-Benzo(1,3)dioxol-5-ylmethoxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide;

3-(4-((1R,3R,4R)-3-(1-((E)-Benzo(1,3)dioxol-5-ylmethoxyimino)-ethyl)-4-hydroxy-cyclopentyloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide;

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3-(4-((2S,4S,5R)-5-(1-((E)-Benzo[1,3]dioxol-5-ylmethoxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide;

3-(4-((2S,4S,5R)-5-(((E)-Benzo(1,3)dioxol-5-ylmethoxyimino)-methyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide;

3-(4-((1R,2S,3R,4R)-4-(((E)-2,4-Dichloro-benzyloxyimino)-methyl)-2,3-dihydroxy-cyclopentyloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide;

3-(4-((1R,2S,3R,4R)-4-(1-((E)-2-Fluoro-benzyloxyimino)-ethyl)-2,3-dihydroxy-cyclopentyloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide;

3-(4-((2S,3S,4S,5R)-5-(3-(2,4-Dichloro-phenoxy)-1-hydroxymethyl-(E)-propenyl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide;

3-(4-((2S,4S,5R)-5-(3-(2,4-Dichloro-phenoxy)-1-hydroxymethyl-(E)-propenyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide;

3-(4-((1R,2S,3R,4S)-4-(3-(2,4-Dichloro-phenoxy)-(E)-propenyl)-2,3-dihydroxy-cyclopentyloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide;

3-(4-((2S,3S,4R,5R)-5-(1-((E)-3,4-Difluoro-benzyloxyimino)-ethyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide;

3-(4-((2S,3R,4R,5R)-5-(1-((E)-3-Chloro-benzyloxyimino)-ethyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide;

3-(4-((2S,3R,4R,5R)-5-(3-(3,4-Difluoro-phenoxy)-1-methyl-(E)-propenyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide;

3-(4-((2S,4S,5R)-5-(1-((E)-4-Fluoro-benzyloxyimino)-propyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide;

3-(4-((2S,4S,5R)-5-(3-(3-Chloro-phenoxy)-1-ethyl-(E)-propenyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide;

3-(4-((2S,3S,4R,5R)-5-(1-((E)-2-Fluoro-benzyloxyimino)-ethyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide;

3-(4-((2S,3S,4R,5R)-5-(3-(3-Chloro-phenoxy)-1-methyl-(E)-propenyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide;

3-(4-((2S,4S,5R)-5-(3-(3-Chloro-phenoxy)-1-methyl-(Z)-propenyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-fluoro-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide;

3-(4-((2S,4S,5R)-5-(3-(2,3-Dichloro-5-fluoro-phenoxy)-1-ethyl-(Z)-propenyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide;

3-(4-((2S,3S,4R,5R)-5-(3-(3,4-Difluoro-phenoxy)-1-ethyl-(Z)-propenyl)-3-fluoro-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide;

3-(4-((2S,3R,4S,5R)-3-Amino-5-(1-((E)-3,4-difluoro-benzyloxyimino)-ethyl)-4-hydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide;

3-(4-((2S,3S,4R,5R)-5-(3-(3-Chloro-phenoxy)-1-methyl-(Z)-propenyl)-3,4-dihydroxy-3-methyl-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide;

3-(4-((2S,3S,4S,5R)-5-(5S-(3-Chloro-phenyl)-2,3-dimethyl-isoxazolidin-3-yl)-3,4-dihydroxy-tetrahydro-furan-2-yloxy)-3-hydroxy-phenyl)-2-methyl-N-((3aS,4R,5R,6S,7R,7aR)-4,6,7-trihydroxy-hexahydro-benzo(1,3)dioxol-5-yl)-(2E)-acrylamide;

and the pharmaceutically acceptable salts, prodrugs and solvates of the foregoing compounds.