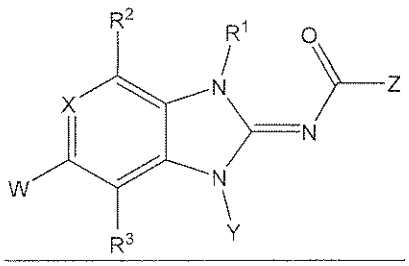
SUMMARY OF THE INVENTION

[005a] In one aspect, there is provided a compound of Formula I:



I

or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, or a stereoisomer of any of the foregoing, wherein:

R^1 is -H;

R^2 is -H;

R^3 is –H;

X is selected from CR^4;

R^4 is –H;

Y is selected from a C_3-C_{12} cycloalkyl or a 3-10 membered heterocyclyl comprising 1, 2, or 3 heteroatoms selected from O, S, or N; wherein the C_3-C_{12} cycloalkyl and the 3-10 membered heterocyclyl may be monocyclic, bicyclic, or tricyclic, and further wherein the C_3-C_{12} cycloalkyl and the 3-10 membered heterocyclyl comprise a substituent selected from -C(=O)NH_2, -C(=O)NH($(C_1$-$C_6)$alkyl), -C(=O)NH-$(C_1$-$C_4)$alkylene-CF_3, -C(=O)NH-$(C_1$-$C_4)$alkylene-F, -C(=O)NH-$(C_2$-$C_4)$alkenyl, -C(=O)N($(C_1$-$C_6)$alkyl)$_2$, -C(=O)NH-OH ,-C(=O)NH-O-$(C_1$-$C_6)$alkyl, -C(=O)NH-Y", -C(=O)-$(C_1$-$C_4)$alkylene-CF_3, -C(=O)N-$(C_1$-$C_4)$alkylene-F, -C(=O)-$(C_2$-$C_4)$alkenyl, -C(=O)-$(C_1$-$C_4)$alkylene-NH_2, -C(=O)-$(C_1$-$C_4)$alkylene-NH($(C_1$-$C_4)$alkyl), -C(=O)-$(C_1$-$C_4)$alkylene-N($(C_1$-$C_4)$alkyl)$_2$, -C(=O)NH-$(C_1$-$C_4)$alkylene-OH, -C(=O)NH-$(C_1$-$C_4)$alkylene-O-$(C_1$-$C_6)$alkyl, -C(=O)NH-$(C_1$-$C_4)$alkylene-Y", -C(=O)-$(C_1$-$C_6)$alkyl, -C(=O)-Y", -CO_2H, -C(=O)-O-$(C_1$-$C_6)$alkyl, -C(=O)NH-$(C_1$-$C_4)$alkylene-NH_2, -C(=O)NH-$(C_1$-$C_4)$alkylene-NH($(C_1$-$C_6)$alkyl), and -C(=O)NH-$(C_1$-$C_4)$alkylene-N($(C_1$-$C_6)$alkyl)$_2$, -$(C_1$-$C_4)$alkylene-NH-C(=O)-$(C_1$-$C_6)$alkyl; and

wherein Y optionally further comprises 1 or 2 substituents selected from Y', -F, -Cl, -Br, -I, -C≡N, -NO_2, -OH, -O-(C_1-C_6)alkyl, -SH, -S-(C_1-C_6)alkyl, -OCF_3, -$OCHF_2$, -CF_3, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -NH_2, -NH((C_1-C_4)alkyl), -N((C_1-C_4)alkyl)$_2$, -$NHSO_2$-(C_1-C_6)alkyl, -NHC(=O)-(C_1-C_6)alkyl, -C(=O)NH_2, -C(=O)NH((C_1-C_6)alkyl), -C(=O)NH-(C_1-C_4)alkylene-CF_3, -C(=O)NH-(C_1-C_4)alkylene-F, -C(=O)NH-(C_2-C_4)alkenyl, -C(=O)N((C_1-C_6)alkyl)$_2$, -C(=O)NH-OH ,-C(=O)NH-O-(C_1-C_6)alkyl, -C(=O)NH-Y", -C(=O)-(C_1-C_4)alkylene-CF_3, -C(=O)N-(C_1-C_4)alkylene-F, -C(=O)-(C_2-C_4)alkenyl, -C(=O)-(C_1-C_4)alkylene-NH_2, -C(=O)-(C_1-C_4)alkylene-NH((C_1-C_4)alkyl), -C(=O)-(C_1-C_4)alkylene-N((C_1-C_4)alkyl)$_2$, -C(=O)NH-(C_1-C_4)alkylene-OH, -C(=O)NH-(C_1-C_4)alkylene-O-(C_1-C_6)alkyl, -C(=O)NH-(C_1-C_4)alkylene-Y", -C(=O)-(C_1-C_6)alkyl, -C(=O)-Y", -CO_2H, -C(=O)-O-(C_1-C_6)alkyl, -C(=O)NH-(C_1-C_4)alkylene-NH_2, -C(=O)NH-(C_1-C_4)alkylene-NH((C_1-C_6)alkyl), and -C(=O)NH-(C_1-C_4)alkylene-N((C_1-C_6)alkyl)$_2$, -SO_2NH_2, -SO_2NH((C_1-C_6)alkyl), -SO_2N((C_1-C_6)alkyl)$_2$, -SO_2NH((C_2-C_4)alkenyl), -SO_2NH((C_2-C_4)alkynyl), -SO_2NH-Y", -SO_2NH-(C_1-C_4)alkylene-OH, -SO_2NH-(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2-Y", -SO-(C_1-C_6)alkyl, -(C_1-C_4)alkylene-NH-C(=O)-(C_1-C_6)alkyl, -(C_1-C_4)alkylene-NH-(C_1-C_6)alkyl, -(C_1-C_4)alkylene-N((C_1-C_6)alkyl)$_2$ -(C_1-C_4)alkylene-OH, -(C_1-C_4)alkylene-O-(C_1-C_6)alkyl, -(C_1-C_4)alkylene-C(=O)-(C_1-C_6)alkyl, -(C_1-C_4)alkylene-C(=O)-O-(C_1-C_6)alkyl, or -(C_1-C_4)alkylene-C(=O)-OH, wherein two substituents on a carbon ring member of the Y cycloalkyl or heterocyclyl may join to form a 3-7 membered cycloalkyl group or a 3-7 membered heterocyclyl group that comprises 1 to 3 heteroatoms selected from N, O, or S; and further wherein 1 or 2 carbon atom ring members of the 3-7 membered cycloalkyl or the 3-7 membered heterocyclyl group formed from the two substituents on the carbon ring member of the Y cycloalkyl or heterocyclyl may be double bonded to an O atom;

Y' may be absent or is a C_6-C_{10} aryl, a 5-10 membered heteroaryl comprising 1, 2, 3, or 4 heteroatoms independently selected from O, S, or N, or a 3-7 membered heterocyclyl comprising 1, 2, or 3 heteroatoms selected from O, S, or N, wherein the C_6-C_{10} aryl, the 5-10 membered heteroaryl, or the 3-7 membered heterocyclyl Y' groups are unsubstituted or are optionally

substituted with 1, 2, or 3 substituents independently selected from –F, -Cl, -Br, -I, -C≡N, -NO_2, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_1-C_4)alkylene-OH, -NH_2, -NH((C_1-C_4)alkyl), -N((C_1-C_4)alkyl)$_2$, -C(=O)NH_2, -C(=O)NH((C_1-C_4)alkyl), -C(=O)N((C_1-C_4)alkyl)$_2$, -SO_2NH_2, -SO_2NH((C_1-C_4)alkyl), -SO_2N((C_1-C_4)alkyl)$_2$, -$NHSO_2$-(C_1-C_4)alkyl, -NHC(=O)-(C_1-C_4)alkyl, -SO_2-(C_1-C_6)alkyl, -SO-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-NH-C(=O)-(C_1-C_4)alkyl, -CF_3, -C(=O)-(C_1-C_4)alkyl, -CO_2H, -C(=O)-O-(C_1-C_4)alkyl, -C(=O)NH-(C_1-C_4)alkylene-NH_2, -C(=O)NH-(C_1-C_4)alkylene-NH((C_1-C_4)alkyl), -C(=O)NH-(C_1-C_3)alkylene-N((C_1-C_4)alkyl)$_2$, -C(=O)NH-(C_1-C_4)alkylene-OH, -C(=O)NH-(C_1-C_4)alkylene-CF_3, -C(=O)NH-(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-C(=O)-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-C(=O)-O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-C(=O)-OH, -OH, -O-(C_1-C_6)alkyl, -SH, -S-(C_1-C_6)alkyl, -OCF_3, or -$OCHF_2$;

Y" may be absent or is selected from a C_3-C_{10} cycloalkyl; a 3-10 membered heterocyclyl comprising 1, 2, or 3 heteroatoms selected from N, O, and S; a C_6-C_{10} aryl; or a 5-10 membered heteroaryl comprising 1, 2, 3, or 4 heteroatoms independently selected from N, O, or S; wherein the C_3-C_{10} cycloalkyl and the 3-10 membered heterocyclyl may be monocyclic or bicyclic, and further wherein the C_3-C_{10} cycloalkyl, the 3-10 membered heterocyclyl, the C_6-C_{10} aryl, or the 5-10 membered heteroaryl Y" groups are unsubstituted or are optionally substituted with 1, 2, or 3 substituents independently selected from –F, -Cl, -Br, -I, -C≡N, -NO_2, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_1-C_4)alkylene-OH, -NH_2, -NH((C_1-C_4)alkyl), -N((C_1-C_4)alkyl)$_2$, -C(=O)NH_2, -C(=O)NH((C_1-C_4)alkyl), -C(=O)N((C_1-C_4)alkyl)$_2$, -SO_2NH_2, -SO_2NH((C_1-C_4)alkyl), -SO_2N((C_1-C_4)alkyl)$_2$, -$NHSO_2$-(C_1-C_4)alkyl, -NHC(=O)-(C_1-C_4)alkyl, -SO_2-(C_1-C_6)alkyl, -SO-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-NH-C(=O)-(C_1-C_4)alkyl, -CF_3, -C(=O)-(C_1-C_4)alkyl, -CO_2H, -C(=O)-O-(C_1-C_4)alkyl, -C(=O)NH-(C_1-C_4)alkylene-NH_2, -C(=O)NH-(C_1-C_4)alkylene-NH((C_1-C_4)alkyl), -C(=O)NH-(C_1-C_4)alkylene-N((C_1-C_4)alkyl)$_2$, -C(=O)NH-(C_1-C_4)alkylene-OH, -C(=O)NH-(C_1-C_4)alkylene-CF_3, -C(=O)NH-(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-C(=O)-(C_1-C_4)alkyl, -(C_1-

C_4)alkylene-C(=O)-O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-C(=O)-OH, -OH, -O-(C_1-C_6)alkyl, -SH, -S-(C_1-C_6)alkyl, -OCF_3, or -$OCHF_2$;

W is selected from -$(CR^aR^{a'})_q$-O-(C_1-C_6)alkyl, -$(CR^aR^{a'})_q$-O-W', -O-$(CR^aR^{a'})_q$-W', -O-$(CR^aR^{a'})_q$-OH, -O-$(CR^aR^{a'})_q$-O-(C_1-C_6)alkyl, -$(CR^aR^{a'})_q$-O-$(CR^aR^{a'})_q$-OH, -$(CR^aR^{a'})_q$-O-$(CR^aR^{a'})_q$-O-(C_1-C_6)alkyl, -$(CR^aR^{a'})_q$-SH, -$(CR^aR^{a'})_q$-S-(C_1-C_6)alkyl, -$(CR^aR^{a'})_q$-S-W', -S-$(CR^aR^{a'})_q$-W', -$(CR^aR^{a'})_q$-$S(O)_2$-(C_1-C_6)alkyl, -$(CR^aR^{a'})_q$-$S(O)_2$-W', -$S(O)_2$-$(CR^aR^{a'})_q$-W', -$(CR^aR^{a'})_q$-NH_2, -$(CR^aR^{a'})_q$-NH-(C_1-C_6)alkyl, -$(CR^aR^{a'})_q$-N-((C_1-C_6)alkyl,)$_2$, -$(CR^aR^{a'})_q$-N^+-((C_1-C_6)alkyl,)$_3$, -$(CR^aR^{a'})_q$-NH-W', -$(CR^aR^{a'})_q$-NH-$(CR^aR^{a'})_q$-OH, -NH-$(CR^aR^{a'})_q$-W', or -$(CR^aR^{a'})_q$-W';

W' may be absent or is selected from a C_3-C_{10} cycloalkyl; a 3-10 membered heterocyclyl comprising 1, 2, or 3 heteroatoms selected from N, O, and S; a C_6-C_{10} aryl; or a 5-10 membered heteroaryl comprising 1, 2, 3, or 4 heteroatoms independently selected from N, O, or S; wherein the C_3-C_{10} cycloalkyl and the 3-10 membered heterocyclyl may be monocyclic or bicyclic, and further wherein the C_3-C_{10} cycloalkyl, the 3-10 membered heterocyclyl, the C_6-C_{10} aryl, or the 5-10 membered heteroaryl W' groups are unsubstituted or are optionally substituted with 1, 2, 3, or 4 substituents independently selected from –F, -Cl, -Br, -I, -C≡N, -NO_2, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_1-C_4)alkylene-OH, -NH_2, -NH((C_1-C_4)alkyl), -N((C_1-C_4)alkyl)$_2$, -$CH(CF_3)(OH)$, -(C_1-C_4)alkylene-NH_2, -(C_1-C_4)alkylene-NH((C_1-C_4)alkyl), -(C_1-C_4)alkylene-NH-(C_1-C_4)alkylene-CF_3, -(C_1-C_4)alkylene-N((C_1-C_4)alkyl)$_2$, -C(=O)NH_2, -C(=O)NH((C_1-C_4)alkyl), -C(=O)N((C_1-C_4)alkyl)$_2$, -SO_2NH_2, -SO_2NH((C_1-C_4)alkyl), -SO_2N((C_1-C_4)alkyl)$_2$, -$NHSO_2$-(C_1-C_4)alkyl, -NHC(=O)-(C_1-C_4)alkyl, -SO_2-(C_1-C_6)alkyl, -SO-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-NH-C(=O)-(C_1-C_4)alkyl, -CF_3, -C(=O)-(C_1-C_4)alkyl, -CO_2H, -C(=O)-O-(C_1-C_4)alkyl, -C(=O)NH-(C_1-C_4)alkylene-NH_2, -C(=O)NH-(C_1-C_4)alkylene-NH((C_1-C_4)alkyl), -C(=O)NH-(C_1-C_4)alkylene-N((C_1-C_4)alkyl)$_2$, -C(=O)NH-(C_1-C_4)alkylene-OH, -C(=O)NH-(C_1-C_4)alkylene-CF_3, -C(=O)NH-(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-C(=O)-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-C(=O)-O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-C(=O)-OH, -(C_1-C_4)alkylene-OH, -OH, -O-(C_1-C_6)alkyl, -SH, -S-(C_1-C_6)alkyl, -SO_3H, -OCF_3, -$OCHF_2$, or –C(=O)-W"; and further wherein W' may include 0, 1, or 2 =O

groups when W' is a C_3-C_{10} cycloalkyl or a 3-10 membered heterocyclyl, and further wherein the =O groups may be bonded to a ring carbon atom or a ring S atom;

W" may be absent or is selected from a C_3-C_{10} cycloalkyl; a 3-10 membered heterocyclyl comprising 1, 2, or 3 heteroatoms selected from N, O, and S; a C_6-C_{10} aryl; or a 5-10 membered heteroaryl comprising 1, 2, 3, or 4 heteroatoms independently selected from N, O, or S; wherein the C_3-C_{10} cycloalkyl and the 3-10 membered heterocyclyl may be monocyclic or bicyclic, and further wherein the C_3-C_{10} cycloalkyl, the 3-10 membered heterocyclyl, the C_6-C_{10} aryl, or the 5-10 membered heteroaryl W" groups are unsubstituted or are optionally substituted with 1, 2, 3, or 4 substituents independently selected from –F, -Cl, -Br, -I, -C≡N, -NO_2, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -OH, -NH_2, -NH((C_1-C_4)alkyl), -N((C_1-C_4)alkyl)$_2$, -CF_3, -CO_2H, -C(=O)-O-(C_1-C_4)alkyl, -SH, -S-(C_1-C_6)alkyl, -OCF_3, or -$OCHF_2$; and further wherein W" may include 0, 1, or 2 =O groups when W" is a C_3-C_{10} cycloalkyl or a 3-10 membered heterocyclyl, and further wherein the =O groups may be bonded to a ring carbon atom or a ring S atom;

the subscript q is, in each instance, independently selected from 0, 1, 2, 3, or 4;

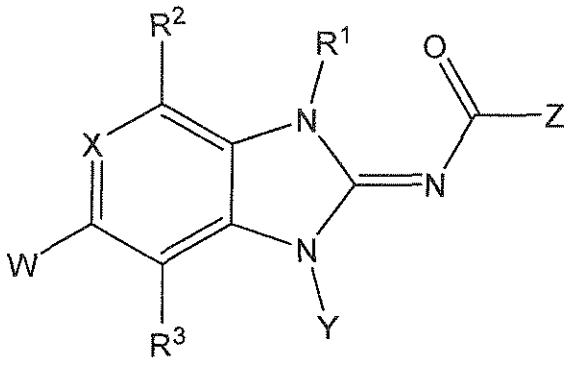
R^a is, in each instance, independently selected from –H, -CH_3, -CH_2CH_3, -F, -CF_3, or -C≡N;

$R^{a'}$ is, in each instance, independently selected from –H, -CH_3, -CH_2CH_3, -F, -CF_3, or -C≡N; or R^a and $R^{a'}$ may join to form a cyclopropyl ring together with the carbon atom to which they are attached;

Z is selected from -OMe or -NH-cyclohexyl; or a phenyl, pyridyl, benzothiophenyl, thiazolyl, pyradizinyl, pyrimidinyl, indolyl, cyclohexyl, morpholinyl, pyrrolidinyl, piperazinyl, or piperidinyl group; wherein the –NH-cyclohexyl, phenyl, pyridyl, benzothiophenyl, thiazolyl, pyradizinyl, pyrimidinyl, indolyl, cyclohexyl, morpholinyl, pyrrolidinyl, piperazinyl, or piperidinyl group is unsubstituted or is optionally substituted with 1, 2, or 3 substituents independently selected from –F, -Cl, -Br, -I, -C≡N, -NO_2, -CF_3, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_1-C_4)alkylene-OH, -NH_2, -NH((C_1-C_6)alkyl), -N((C_1-C_6)alkyl)$_2$, -C(=O)NH_2, -C(=O)NH((C_1-C_6)alkyl), -C(=O)N((C_1-C_6)alkyl)$_2$, -SO_2NH_2, -SO_2NH((C_1-C_6)alkyl), -SO_2N((C_1-

C_6)alkyl)$_2$, -SO_2NH((C_2-C_6)alkenyl), -SO_2NH((C_2-C_6)alkynyl), -SO_2NH-(C_1-C_4)alkylene-OH, -SO_2NH-(C_1-C_4)alkylene-O-(C_1-C_6)alkyl, -NHSO_2-(C_1-C_6)alkyl, -NHC(=O)-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO-(C_1-C_6)alkyl, -(C_1-C_4)alkylene-NH-C(=O)-(C_1-C_6)alkyl, -C(=O)-(C_1-C_6)alkyl, -CO_2H, -C(=O)-O-(C_1-C_6)alkyl, -C(=O)NH-(C_1-C_4)alkylene-NH_2, -C(=O)NH-(C_1-C_4)alkylene-NH((C_1-C_6)alkyl), -C(=O)NH-(C_1-C_4)alkylene-N((C_1-C_6)alkyl)$_2$, -(C_1-C_4)alkylene-C(=O)-(C_1-C_6)alkyl, -(C_1-C_4)alkylene-C(=O)-O-(C_1-C_6)alkyl, -(C_1-C_4)alkylene-C(=O)-OH, -OH, -O-(C_1-C_6)alkyl, -SH, -S-(C_1-C_6)alkyl, -OCF_3, or -$OCHF_2$.

[006] In one example, the disclosure~~aspect, the invention~~ provides a compound of Formula I:



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or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, a stereoisomer of any of the foregoing, or a mixture thereof,

wherein:

R^1 is -H;

R^2 is -H;

R^3 is selected from –H, -F, -Cl, -Br, -I; -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -CF_3, -OH, -OCF_3, -O-(C_1-C_6)alkyl, -$OCHF_2$, -SH, -S-(C_1-C_6)alkyl, -NH_2, -N(H)-(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, -NO_2, -C≡N, -C(=O)OH, -C(=O)O-(C_1-C_6)alkyl, -C(=O)NH_2, -C(=O)N(H)-(C_1-C_6)alkyl, -C(=O)N((C_1-C_6)alkyl)$_2$, -N(H)-C(=O)-(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)-C(=O)-(C_1-C_6)alkyl, -(C_1-C_4)alkylene-OH, -(C_1-C_4)alkylene-NH_2, -(C_1-C_4)alkylene-N(H)-(C_1-C_6)alkyl, –(C_1-C_4)alkylene-N((C_1-C_6)alkyl)$_2$, or phenyl optionally substituted with 1, 2, or 3 substituents selected from -F, -Cl, -Br, -I; -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -CF_3, -OH, -OCF_3, -O-(C_1-C_6)alkyl, -$OCHF_2$, -SH, -S-(C_1-C_6)alkyl, -NH_2, -N(H)-(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$,

$-NO_2$, -C≡N, -C(=O)OH, -C(=O)O-(C_1-C_6)alkyl, -C(=O)NH_2, -C(=O)N(H)-(C_1-C_6)alkyl, or -C(=O)N((C_1-C_6)alkyl)$_2$;

X is selected from CR^4 or N;

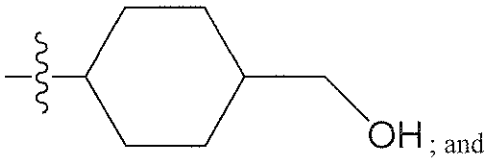
R^4 is absent if X is N, or is selected from –H, -F, -Cl, -Br, -I; -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, $-CF_3$, -OH, $-OCF_3$, -O-(C_1-C_6)alkyl, $-OCHF_2$, -SH, -S-(C_1-C_6)alkyl, $-NH_2$, -N(H)-(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, $-NO_2$, -C≡N, -C(=O)OH, -C(=O)O-(C_1-C_6)alkyl, -C(=O)NH_2, -C(=O)N(H)-(C_1-C_6)alkyl, -C(=O)N((C_1-C_6)alkyl)$_2$, -(C_1-C_4)alkylene-OH, -(C_1-C_4)alkylene-NH_2, -(C_1-C_4)alkylene-N(H)-(C_1-C_6)alkyl, –(C_1-

C_6)alkyl, -(C_1-C_4)alkylene-C(=O)-OH, -OH, -O-(C_1-C_6)alkyl, -SH, -S-(C_1-C_6)alkyl, $-OCF_3$, or $-OCHF_2$;

W is not –H, -F, -Cl, -Br, -I, or unsubstituted -(C_1-C_6)alkyl if X is CR^4;

Y is not unsubstituted cyclopropyl, cyclobutyl, or cyclopentyl if W is -H, -F, -Cl, -Br, -I, or -(C_1-C_6)alkyl;

W is not $–CH_2OH$ or $–CH_2O(C_1$-C_4alkyl) if Y is a group of formula



; and

W is not –SH, -OH, –S-(C_1-C_6)alkyl), or –S-(C_1-C_6)alkyl) if Z is –O-(C_1-C_6)alkyl);

wherein the symbol ∿∿∿, when drawn across a bond, indicates the point of attachment to the rest of the molecule.

[007] In some ~~embodiments~~examples, X is N.

[008] In some ~~embodiments~~examples, X is CR^4. In some such ~~embodiments~~examples, R^4 is –H.

[009] In some ~~embodiments~~examples, R^3 is -H.

[010] In some ~~embodiments~~examples, Z is selected from -OMe or -NH-cyclohexyl; or an unsubstituted or substituted phenyl, pyridyl, benzothiophenyl, thiazolyl, pyradizinyl, pyrimidinyl, indolyl, cyclohexyl, morpholinyl, pyrrolidinyl, piperazinyl, piperidinyl, isothiazolyl, or thiomorpholinyl group. In some such ~~embodiments~~examples, Z is selected from -OMe or -NH-cyclohexyl; or an unsubstituted or substituted phenyl, pyridyl, benzothiophenyl, thiazolyl, pyradizinyl, pyrimidinyl, indolyl, cyclohexyl, morpholinyl, pyrrolidinyl, piperazinyl, or piperidinyl.

[011] In some ~~embodiments~~examples, Z is an unsubstituted or substituted phenyl, pyridyl, benzothiophenyl, thiazolyl, pyradizinyl, pyrimidinyl, indolyl, cyclohexyl, morpholinyl, pyrrolidinyl, piperazinyl, piperidinyl, isothiazolyl, or thiomorpholinyl group. In some ~~embodiments~~examples, Z is an unsubstituted or substituted phenyl, pyridyl, benzothiophenyl, thiazolyl, pyradizinyl, pyrimidinyl, indolyl, cyclohexyl, morpholinyl, pyrrolidinyl, piperazinyl, or piperidinyl group. In some such ~~embodiments~~examples, Z is a substituted phenyl, pyridyl, benzothiophenyl, thiazolyl, pyradizinyl, pyrimidinyl, indolyl, cyclohexyl, morpholinyl, pyrrolidinyl, piperazinyl, or piperidinyl group.

[012] In some ~~embodiments~~examples, Z is an unsubstituted or substituted phenyl or pyridyl. In some such ~~embodiments~~examples, Z is a substituted phenyl or pyridyl. In some other such ~~embodiments~~examples, Z is a substituted phenyl.

[013] In some ~~embodiments~~examples, Y is an unsubstituted or substituted cycloheptyl, cyclohexyl, cyclopentyl, cyclobutyl, piperidinyl, pyrrolidinyl, azetidinyl, adamantyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[4.1.1]octyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, or bicyclo[2.1.1]hexyl. In some such ~~embodiments~~examples, Y is a substituted cycloheptyl, cyclohexyl, cyclopentyl, cyclobutyl, piperidinyl, pyrrolidinyl, adamantyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[4.1.1]octyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, or bicyclo[2.1.1]hexyl group. In some such ~~embodiments~~examples, Y is an unsubstituted or substituted cyclohexyl. In some such ~~embodiments~~examples, Y is a substituted cyclohexyl. In other such ~~embodiments~~examples, Y is an unsubstituted or substituted adamantyl. In some such ~~embodiments~~examples, Y is an unsubstituted adamantyl. In other ~~embodiments~~examples, Y is a substituted adamantyl. In other such ~~embodiments~~examples, Y is an unsubstituted or substituted cyclobutyl. In some such ~~embodiments~~examples, Y is a substituted cyclobutyl. In still other ~~embodiments~~examples, Y is an unsubstituted or substituted cyclopentyl or cycloheptyl. In some such ~~embodiments~~examples Y is a substituted cyclopentyl or cycloheptyl. In still other ~~embodiments~~examples, Y is an unsubstituted or substituted piperidinyl. In some such ~~embodiments~~examples, Y is a substituted piperidinyl. In some ~~embodiments~~examples where Y is substituted, Y is substituted with a group that includes a carbonyl (C=O) functional group. Examples include, but are not limited to ketones, esters, and amides.

[014] In some ~~embodiments~~examples, W is selected from $-CH_2OH$, $-CH_2OCH_3$, $-CH_2OCH_2CH_2OH$, $-CH_2OCH_2CH_2OCH_3$, $-OCH_2CH_2OH$, $-OCH_2CH_2OMe$, -W', $-CH_2W'$, -OW', $-OCH_2W'$, $-OCH_2CH_2W'$, $-OCH_2CH_2CH_2W'$, -NHW', $-NHCH_2W'$, $-NHCH_2CH_2W'$, $-NHCH_2CH_2CH_2W'$, or -W'-C(=O)-W"; wherein W', if present, is selected from a 3-10 membered heterocyclyl comprising 1 or 2 heteroatoms selected from N, O, and S; a C_6-C_{10} aryl; or a 5-10 membered heteroaryl comprising 1, 2, 3, or 4 heteroatoms independently selected from N, O, or S; wherein the 3-10 membered heterocyclyl W' group may be monocyclic or bicyclic, and further wherein the 3-10 membered heterocyclyl, the C_6-C_{10} aryl, or the 5-10 membered heteroaryl W' groups are unsubstituted or are substituted with 1, 2, 3, or 4 substituents independently selected from –F, -Cl, -Br, -(C_1-C_6)alkyl, $-CH(CF_3)(OH)$, -(C_1-C_4)alkylene-NH_2, -(C_1-C_4)alkylene-NH-(C_1-C_4)alkylene-CF_3, $-C(=O)NH_2$, $-SO_2$-(C_1-C_6)alkyl, $-CF_3$, $-CO_2H$,

-(C_1-C_4)alkylene-C(=O)-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-C(=O)-O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-C(=O)-OH, -(C_1-C_4)alkylene-OH, -OH, -O-(C_1-C_6)alkyl, or -SO_3H; and further wherein W' may include 0, 1, or 2 =O groups when W' is a 3-10 membered heterocyclyl, and further wherein the =O groups may be bonded to a ring carbon atom or a ring S atom; and further wherein W", if present, is a 3-10 membered heterocyclyl comprising 1, 2, or 3 heteroatoms selected from N, O, and S, wherein the 3-10 membered heterocyclyl W" group may be monocyclic or bicyclic, and further wherein the 3-10 membered heterocyclyl W" group is unsubstituted or is optionally substituted with 1, 2, 3, or 4 substituents independently selected from –F, -Cl, -Br, -I, -C≡N, -NO_2, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -OH, -NH_2, -NH((C_1-C_4)alkyl), -N((C_1-C_4)alkyl)$_2$, -CF_3, -CO_2H, -C(=O)-O-(C_1-C_4)alkyl, -SH, -S-(C_1-C_6)alkyl, -OCF_3, or -$OCHF_2$, or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, a stereoisomer of any of the foregoing, or a mixture thereof.

[015] In some ~~embodiments~~examples, W is selected from -W', -CH_2W', -OW', -OCH_2W', -OCH_2CH_2W', -$OCH_2CH_2CH_2$W', -NHW', -$NHCH_2$W', -$NHCH_2CH_2$W', –$NHCH_2CH_2CH_2$W', or -W'-C(=O)-W"; wherein W', is selected from a 3-10 membered heterocyclyl comprising 1 or 2 heteroatoms selected from N, O, and S; a C_6-C_{10} aryl; or a 5-10 membered heteroaryl comprising 1, 2, 3, or 4 heteroatoms independently selected from N, O, or S; wherein the 3-10 membered heterocyclyl W' group may be monocyclic or bicyclic, and further wherein the 3-10 membered heterocyclyl, the C_6-C_{10} aryl, or the 5-10 membered heteroaryl W' groups are unsubstituted or are substituted with 1, 2, 3, or 4 substituents independently selected from –F, -Cl, -Br, -(C_1-C_6)alkyl, -CH(CF_3)(OH), -(C_1-C_4)alkylene-NH_2, -(C_1-C_4)alkylene-NH-(C_1-C_4)alkylene-CF_3, -C(=O)NH_2, -SO_2-(C_1-C_6)alkyl, -CF_3, -CO_2H, -(C_1-C_4)alkylene-C(=O)-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-C(=O)-O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-C(=O)-OH, -(C_1-C_4)alkylene-OH, -OH, -O-(C_1-C_6)alkyl, or -SO_3H; and further wherein W' may include 0, 1, or 2 =O groups when W' is a 3-10 membered heterocyclyl, and further wherein the =O groups may be bonded to a ring carbon atom or a ring S atom; and further wherein W", if present, is a 3-10 membered heterocyclyl comprising 1, 2, or 3 heteroatoms selected from N, O, and S, wherein the 3-10 membered heterocyclyl W" group may be monocyclic or bicyclic, and further wherein the 3-10 membered heterocyclyl W" group is unsubstituted or is optionally substituted with 1, 2, 3, or 4 substituents independently selected from –F, -Cl, -Br, -I, -C≡N, -NO_2,

-(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -OH, -NH_2, -NH((C_1-C_4)alkyl), -N((C_1-C_4)alkyl)$_2$, -CF_3, -CO_2H, -C(=O)-O-(C_1-C_4)alkyl, -SH, -S-(C_1-C_6)alkyl, -OCF_3, or -$OCHF_2$.

[016] In some ~~embodiments~~examples, W is not –H, -F, -Cl, –OH, or -OMe.

[017] In some ~~embodiments~~examples of any of those described above, the compound is a pharmaceutically acceptable salt of the compound, a tautomer of the compound, a pharmaceutically acceptable salt of the tautomer, a stereoisomer of any of the foregoing, or is a mixture of any of these. In some such ~~embodiments~~examples, the compound is a tautomer. In some such ~~embodiments~~examples, the compound is a pharmaceutically acceptable salt of the tautomer. In still other ~~embodiments~~examples, the compound is a single stereoisomer whereas in other ~~embodiments~~examples, the compound is a mixture of enantiomers or is a mixture of stereoisomers and such a mixture may include equal or unequal amount of specific stereioisomers. In some ~~embodiments~~examples, the compound is a racemic mixture of stereoisomers.

[018] In some ~~embodiments~~examples, the compound is any one of the Example compounds.

[019] In some ~~embodiments~~examples, the compound is a salt. Such salts may be anhydrous or associated with water as a hydrate.

[020] In some ~~embodiments~~examples, the compound is a prodrug.

[021] Also provided are pharmaceutical formulations that include at least one pharmaceutically acceptable carrier, excipient or diluent and a therapeutically effective amount of the compound of any of the ~~embodiments~~examples described herein. In some such ~~embodiments~~examples, the compound is present in an amount effective for the treatment of cancer.

[021a] In another aspect, there is also provided a pharmaceutical composition comprising a therapeutically effective amount of the compound or the pharmaceutically acceptable salt thereof, tautomer thereof, the pharmaceutically acceptable salt of the tautomer, or the stereoisomer of any of the foregoing, as described herein and at least one pharmaceutically acceptable excipient, carrier, or diluent.

[022] Further provided are pharmaceutical formulations that include at least one pharmaceutically acceptable carrier, and a therapeutically effective amount of the composition of matter of any of the ~~embodiments~~examples described herein in combination with at least one additional compound such as a cytotoxic agent or a compound that inhibits another kinase.

[023] In other ~~embodiments~~examples, the ~~invention~~disclosure provides a method of treating cancer. Such methods typically include administering to a subject an effective amount of a compound of any one of the ~~embodiments~~examples or a pharmaceutical composition that includes any of the compounds of any of the ~~embodiments~~examples. In some such ~~embodiments~~examples, the subject has a cancer that expresses an ALK fusion protein, point

mutation, or overexpression. In other such ~~embodiments~~examples, the ALK fusion protein is EML4-ALK fusion protein or NPM-ALK fusion protein. In some ~~embodiments~~examples, the subject is a human cancer patient, and the cancer is selected from adenocarcinoma, lung cancer, non-small cell lung carcinoma, breast cancer, colorectal cancer, lymphoma, neuroblastoma, ovarian cancer, mesothelioma, melanoma, glioblastoma diffuse large B-cell lymphomas, systemic histiocytosis, or inflammatory myofibroblastic tumors. In some such ~~embodiments~~examples, the cancer is non-small cell lung carcinoma (NSCLC). In some ~~embodiments~~examples, the cancer is an EML4-ALK positive cancer or is a NPM-ALK positive cancer.

[024] In still other ~~embodiments~~examples, the ~~invention~~disclosure provides a method of treating a condition where it is desired to inhibit ALK activity. Such methods typically include administering to a subject an effective amount of a compound of any of the ~~embodiments~~examples or a pharmaceutical composition that includes a compound of any of the ~~embodiments~~examples.

[025] In some ~~embodiments~~examples, the compound of any of the ~~embodiments~~examples is used in the preparation of a medicament. In some such ~~embodiments~~examples, the medicament is for use in treating cancer. In some such ~~embodiments~~examples, a medicament is for use in inhibiting ALK. In still other such ~~embodiments~~examples, the medicament is for use in treating a cancer that expresses an ALK fusion protein. In some such ~~embodiments~~examples, the ALK fusion protein is EML4-ALK fusion protein or NPM-ALK fusion protein. In some such ~~embodiments~~examples, the ALK fusion protein is EML4-ALK fusion protein. In other such ~~embodiments~~examples, the ALK fusion protein is NPM-ALK fusion protein.

[026] In some such ~~embodiments~~examples, a compound or pharmaceutical formulation of any of the ~~embodiments~~examples is provided for use in treating cancer. In some such ~~embodiments~~examples, the cancer expresses an ALK fusion protein. In some such ~~embodiments~~examples, the ALK fusion protein is EML4-ALK fusion protein or NPM-ALK fusion protein. In some such ~~embodiments~~examples, the ALK fusion protein is EML4-ALK fusion protein. In other such ~~embodiments~~examples, the ALK fusion protein is NPM-ALK fusion protein. In some ~~embodiments~~examples, a compound or pharmaceutical formulation of any of the ~~embodiments~~examples is provided for use in treating cancer and the cancer is selected from adenocarcinoma, lung cancer, non-small cell lung carcinoma, breast cancer, colorectal cancer, lymphoma, neuroblastoma, ovarian cancer, mesothelioma, melanoma, glioblastoma diffuse large B-cell lymphomas, systemic histiocytosis, or inflammatory myofibroblastic tumors. In some such ~~embodiments~~examples, the cancer is non-small cell lung

carcinoma (NSCLC). In still other ~~embodiments~~examples, a compound or pharmaceutical formulation of any of the ~~embodiments~~examples is provided for use in inhibiting ALK or for use in treating a disease or condition wherein inhibition of ALK is desired.

[027] Other objects, features and advantages of the invention will become apparent to those skilled in the art from the following description and claims.

DETAILED DESCRIPTION OF THE INVENTION

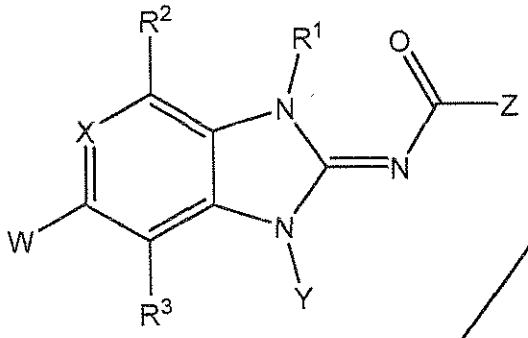
[028] Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are approximations that may vary depending upon the standard deviation found in their respective testing measurements.

[029] As used herein, if any variable occurs more than one time in a chemical formula, its definition on each occurrence is independent of its definition at every other occurrence. If the chemical structure and chemical name conflict, the chemical structure is determinative of the identity of the compound. The compounds of the present disclosure may contain one or more chiral centers and/or double bonds and therefore, may exist as stereoisomers, such as double-bond isomers (i.e., geometric isomers), enantiomers or diastereomers. Accordingly, any chemical structures within the scope of the specification depicted, in whole or in part, with a relative configuration encompass all possible enantiomers and stereoisomers of the illustrated compounds including the stereoisomerically pure form (e.g., geometrically pure, enantiomerically pure or diastereomerically pure) and enantiomeric and stereoisomeric mixtures. Enantiomeric and stereoisomeric mixtures can be resolved into the component enantiomers or stereoisomers using separation techniques or chiral synthesis techniques well known to the skilled artisan.

[030] Certain compounds of the invention may possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, enantiomers, diastereomers, geometric isomers and individual isomers are all intended to be encompassed within the scope of the invention. Furthermore, atropisomers and mixtures thereof such as those resulting from restricted rotation about two aromatic or heteroaromatic rings bonded to

WHAT IS CLAIMED:

1. A compound of Formula I:



I

or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, a stereoisomer of any of the foregoing, or a mixture thereof,

wherein:

R^1 is -H;

R^2 is -H;

R^3 is selected from –H, -F, -Cl, -Br, -I; -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -CF_3, -OH, -OCF_3, -O-(C_1-C_6)alkyl, -$OCHF_2$, -SH, -S-(C_1-C_6)alkyl, -NH_2, -N(H)-(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, -NO_2, -C≡N, -C(=O)OH, -C(=O)O-(C_1-C_6)alkyl, -C(=O)NH_2, -C(=O)N(H)-(C_1-C_6)alkyl, -C(=O)N((C_1-C_6)alkyl)$_2$, -N(H)-C(=O)-(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)-C(=O)-(C_1-C_6)alkyl, -(C_1-C_4)alkylene-OH, -(C_1-C_4)alkylene-NH_2, -(C_1-C_4)alkylene-N(H)-(C_1-C_6)alkyl, –(C_1-C_4)alkylene-N((C_1-C_6)alkyl)$_2$, or phenyl optionally substituted with 1, 2, or 3 substituents selected from -F, -Cl, -Br, -I; -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -CF_3, -OH, -OCF_3, -O-(C_1-C_6)alkyl, -$OCHF_2$, -SH, -S-(C_1-C_6)alkyl, -NH_2, -N(H)-(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, -NO_2, -C≡N, -C(=O)OH, -C(=O)O-(C_1-C_6)alkyl, -C(=O)NH_2, -C(=O)N(H)-(C_1-C_6)alkyl, or -C(=O)N((C_1-C_6)alkyl)$_2$;

X is selected from CR^4 or N;

R^4 is absent if X is N, or is selected from –H, -F, -Cl, -Br, -I; -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -CF_3, -OH, -OCF_3, -O-(C_1-C_6)alkyl, -$OCHF_2$, -SH, -S-(C_1-C_6)alkyl, -NH_2, -N(H)-(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, -NO_2, -C≡N, -C(=O)OH,

-C(=O)O-(C_1-C_6)alkyl, -C(=O)NH_2, -C(=O)N(H)-(C_1-C_6)alkyl, -C(=O)N((C_1-C_6)alkyl)$_2$, -(C_1-C_4)alkylene-OH, -(C_1-C_4)alkylene-NH_2, -(C_1-C_4)alkylene-N(H)-(C_1-C_6)alkyl, or –(C_1-C_4)alkylene-N((C_1-C_6)alkyl)$_2$;

Y is selected from a C_3-C_{12} cycloalkyl or a 3-10 membered heterocyclyl comprising 1, 2, or 3 heteroatoms selected from O, S, or N; wherein the C_3-C_{12} cycloalkyl and the 3-10 membered heterocyclyl may be monocyclic, bicyclic, or tricyclic, and further wherein the C_3-C_{12} cycloalkyl and the 3-10 membered heterocyclyl are unsubstituted or are optionally substituted with 1, 2, or 3 substituents independently selected from –Y', –F, -Cl, -Br, -I, -C≡N, -NO_2, -OH, -O-(C_1-C_6)alkyl, -SH, -S-(C_1-C_6)alkyl, -OCF_3, -$OCHF_2$, -CF_3, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -NH_2, -NH((C_1-C_4)alkyl), -N((C_1-C_4)alkyl)$_2$, -NHSO_2-(C_1-C_6)alkyl, -NHC(=O)-(C_1-C_6)alkyl, -C(=O)NH_2, -C(=O)NH((C_1-C_6)alkyl), -C(=O)NH-(C_1-C_4)alkylene-CF_3, -C(=O)NH-(C_1-C_4)alkylene-F, -C(=O)NH-(C_2-C_4)alkenyl, -C(=O)N((C_1-C_6)alkyl)$_2$, -C(=O)NH-OH ,-C(=O)NH-O-(C_1-C_6)alkyl, -C(=O)NH-Y", -C(=O)-(C_1-C_4)alkylene-CF_3, -C(=O)N-(C_1-C_4)alkylene-F, -C(=O)-(C_2-C_4)alkenyl, -C(=O)-(C_1-C_4)alkylene-NH_2, -C(=O)-(C_1-C_4)alkylene-NH((C_1-C_4)alkyl), -C(=O)-(C_1-C_4)alkylene-N((C_1-C_4)alkyl)$_2$, -C(=O)NH-(C_1-C_4)alkylene-OH, -C(=O)NH-(C_1-C_4)alkylene-O-(C_1-C_6)alkyl, -C(=O)NH-(C_1-C_4)alkylene-Y", -C(=O)-(C_1-C_6)alkyl, -C(=O)-Y", -CO_2H, -C(=O)-O-(C_1-C_6)alkyl, -C(=O)NH-(C_1-C_4)alkylene-NH_2, -C(=O)NH-(C_1-C_4)alkylene-NH((C_1-C_6)alkyl), -C(=O)NH-(C_1-C_4)alkylene-N((C_1-C_6)alkyl)$_2$, -SO_2NH_2, -SO_2NH((C_1-C_6)alkyl), -SO_2N((C_1-C_6)alkyl)$_2$, -SO_2NH((C_2-C_4)alkenyl), -SO_2NH((C_2-C_4)alkynyl), -SO_2NH-Y", -SO_2NH-(C_1-C_4)alkylene-OH, -SO_2NH-(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2-Y", -SO-(C_1-C_6)alkyl, -(C_1-C_4)alkylene-NH-C(=O)-(C_1-C_6)alkyl, -(C_1-C_4)alkylene-NH-(C_1-C_6)alkyl, -(C_1-C_4)alkylene-N((C_1-C_6)alkyl)$_2$ -(C_1-C_4)alkylene-OH, -(C_1-C_4)alkylene-O-(C_1-C_6)alkyl, -(C_1-C_4)alkylene-C(=O)-(C_1-C_6)alkyl, -(C_1-C_4)alkylene-C(=O)-O-(C_1-C_6)alkyl, or -(C_1-C_4)alkylene-C(=O)-OH; wherein two substituents on a carbon ring member of the Y cycloalkyl or heterocyclyl may join to form a 3-7 membered cycloalkyl group or a 3-7 membered heterocyclyl group that comprises 1 to 3 heteroatoms selected from N, O, or S; and further wherein 1 or 2 carbon atom ring members of the 3-7 membered cycloalkyl or the 3-7 membered heterocyclyl group formed from the two substituents on the carbon ring member of the Y cycloalkyl or heterocyclyl may be double bonded to an O atom;

Y' may be absent or is a C_6-C_{10} aryl, a 5-10 membered heteroaryl comprising 1, 2, 3, or 4 heteroatoms independently selected from O, S, or N, or a 3-7 membered

heterocyclyl comprising 1, 2, or 3 heteroatoms selected from O, S, or N, wherein the C_6-C_{10} aryl, the 5-10 membered heteroaryl, or the 3-7 membered heterocyclyl Y' groups are unsubstituted or are optionally substituted with 1, 2, or 3 substituents independently selected from –F, -Cl, -Br, -I, -C≡N, -NO_2, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_1-C_4)alkylene-OH, -NH_2, -NH((C_1-C_4)alkyl), -N((C_1-C_4)alkyl)$_2$, -C(=O)NH_2, -C(=O)NH((C_1-C_4)alkyl), -C(=O)N((C_1-C_4)alkyl)$_2$, -SO_2NH_2, -SO_2NH((C_1-C_4)alkyl), -SO_2N((C_1-C_4)alkyl)$_2$, -NHSO_2-(C_1-C_4)alkyl, -NHC(=O)-(C_1-C_4)alkyl, -SO_2-(C_1-C_6)alkyl, -SO-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-NH-C(=O)-(C_1-C_4)alkyl, -CF_3, -C(=O)-(C_1-C_4)alkyl, -CO_2H, -C(=O)-O-(C_1-C_4)alkyl, -C(=O)NH-(C_1-C_4)alkylene-NH_2, -C(=O)NH-(C_1-C_4)alkylene-NH((C_1-C_4)alkyl), -C(=O)NH-(C_1-C_4)alkylene-N((C_1-C_4)alkyl)$_2$, -C(=O)NH-(C_1-C_4)alkylene-OH, -C(=O)NH-(C_1-C_4)alkylene-CF_3, -C(=O)NH-(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-C(=O)-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-C(=O)-O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-C(=O)-OH, -OH, -O-(C_1-C_6)alkyl, -SH, -S-(C_1-C_6)alkyl, -OCF_3, or -$OCHF_2$;

Y" may be absent or is selected from a C_3-C_{10} cycloalkyl; a 3-10 membered heterocyclyl comprising 1, 2, or 3 heteroatoms selected from N, O, and S; a C_6-C_{10} aryl; or a 5-10 membered heteroaryl comprising 1, 2, 3, or 4 heteroatoms independently selected from N, O, or S; wherein the C_3-C_{10} cycloalkyl and the 3-10 membered heterocyclyl may be monocyclic or bicyclic, and further wherein the C_3-C_{10} cycloalkyl, the 3-10 membered heterocyclyl, the C_6-C_{10} aryl, or the 5-10 membered heteroaryl Y" groups are unsubstituted or are optionally substituted with 1, 2, or 3 substituents independently selected from –F, -Cl, -Br, -I, -C≡N, -NO_2, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_1-C_4)alkylene-OH, -NH_2, -NH((C_1-C_4)alkyl), -N((C_1-C_4)alkyl)$_2$, -C(=O)NH_2, -C(=O)NH((C_1-C_4)alkyl), -C(=O)N((C_1-C_4)alkyl)$_2$, -SO_2NH_2, -SO_2NH((C_1-C_4)alkyl), -SO_2N((C_1-C_4)alkyl)$_2$, -NHSO_2-(C_1-C_4)alkyl, -NHC(=O)-(C_1-C_4)alkyl, -SO_2-(C_1-C_6)alkyl, -SO-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-NH-C(=O)-(C_1-C_4)alkyl, -CF_3, -C(=O)-(C_1-C_4)alkyl, -CO_2H, -C(=O)-O-(C_1-C_4)alkyl, -C(=O)NH-(C_1-C_4)alkylene-NH_2, -C(=O)NH-(C_1-C_4)alkylene-NH((C_1-C_4)alkyl), -C(=O)NH-(C_1-C_4)alkylene-N((C_1-C_4)alkyl)$_2$, -C(=O)NH-(C_1-C_4)alkylene-OH, -C(=O)NH-(C_1-C_4)alkylene-CF_3, -C(=O)NH-(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-C(=O)-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-C(=O)-O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-C(=O)-OH, -OH, -O-(C_1-C_6)alkyl, -SH, -S-(C_1-C_6)alkyl, -OCF_3, or -$OCHF_2$;

W is selected from –H, -F, -Cl, -Br, -I, -(C_1-C_6)alkyl, -($CR^aR^{a'}$)$_q$-OH, -($CR^aR^{a'}$)$_q$-O-(C_1-C_6)alkyl, -($CR^aR^{a'}$)$_q$-O-W', -O-($CR^aR^{a'}$)$_q$-W', -O-($CR^aR^{a'}$)$_q$-OH,

-O-($CR^aR^{a'}$)$_q$-O-(C_1-C_6)alkyl, -($CR^aR^{a'}$)$_q$-O-($CR^aR^{a'}$)$_q$-OH, -($CR^aR^{a'}$)$_q$-O-($CR^aR^{a'}$)$_q$-O-(C_1-C_6)alkyl, -($CR^aR^{a'}$)$_q$-SH, -($CR^aR^{a'}$)$_q$-S-(C_1-C_6)alkyl, -($CR^aR^{a'}$)$_q$-S-W', -S-($CR^aR^{a'}$)$_q$-W', -($CR^aR^{a'}$)$_q$-S(O)$_2$-(C_1-C_6)alkyl, -($CR^aR^{a'}$)$_q$-S(O)$_2$-W', -S(O)$_2$-($CR^aR^{a'}$)$_q$-W', -($CR^aR^{a'}$)$_q$-NH_2, -($CR^aR^{a'}$)$_q$-NH-(C_1-C_6)alkyl, -($CR^aR^{a'}$)$_q$-N-((C_1-C_6)alkyl,)$_2$, -($CR^aR^{a'}$)$_q$-N^+-((C_1-C_6)alkyl,)$_3$, -($CR^aR^{a'}$)$_q$-NH-W', -($CR^aR^{a'}$)$_q$-NH-($CR^aR^{a'}$)$_q$-OH, -NH-($CR^aR^{a'}$)$_q$-W', or -($CR^aR^{a'}$)$_q$-W';

W' may be absent or is selected from a C_3-C_{10} cycloalkyl; a 3-10 membered heterocyclyl comprising 1, 2, or 3 heteroatoms selected from N, O, and S; a C_6-C_{10} aryl; or a 5-10 membered heteroaryl comprising 1, 2, 3, or 4 heteroatoms independently selected from N, O, or S; wherein the C_3-C_{10} cycloalkyl and the 3-10 membered heterocyclyl may be monocyclic or bicyclic, and further wherein the C_3-C_{10} cycloalkyl, the 3-10 membered heterocyclyl, the C_6-C_{10} aryl, or the 5-10 membered heteroaryl W' groups are unsubstituted or are optionally substituted with 1, 2, 3, or 4 substituents independently selected from –F, -Cl, -Br, -I, -C≡N, -NO_2, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_1-C_4)alkylene-OH, -NH_2, -NH((C_1-C_4)alkyl), -N((C_1-C_4)alkyl)$_2$, -CH(CF_3)(OH), -(C_1-C_4)alkylene-NH_2, -(C_1-C_4)alkylene-NH((C_1-C_4)alkyl), -(C_1-C_4)alkylene-NH-(C_1-C_4)alkylene-CF_3, -(C_1-C_4)alkylene-N((C_1-C_4)alkyl)$_2$, -C(=O)NH_2, -C(=O)NH((C_1-C_4)alkyl), -C(=O)N((C_1-C_4)alkyl)$_2$, -SO_2NH_2, -SO_2NH((C_1-C_4)alkyl), -SO_2N((C_1-C_4)alkyl)$_2$, -NHSO_2-(C_1-C_4)alkyl, -NHC(=O)-(C_1-C_4)alkyl, -SO_2-(C_1-C_6)alkyl, -SO-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-NH-C(=O)-(C_1-C_4)alkyl, -CF_3, -C(=O)-(C_1-C_4)alkyl, -CO_2H, -C(=O)-O-(C_1-C_4)alkyl, -C(=O)NH-(C_1-C_4)alkylene-NH_2, -C(=O)NH-(C_1-C_4)alkylene-NH((C_1-C_4)alkyl), -C(=O)NH-(C_1-C_4)alkylene-N((C_1-C_4)alkyl)$_2$, -C(=O)NH-(C_1-C_4)alkylene-OH, -C(=O)NH-(C_1-C_4)alkylene-CF_3, -C(=O)NH-(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-C(=O)-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-C(=O)-O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-C(=O)-OH, -(C_1-C_4)alkylene-OH, -OH, -O-(C_1-C_6)alkyl, -SH, -S-(C_1-C_6)alkyl, -SO_3H, -OCF_3, -$OCHF_2$, or –C(=O)-W"; and further wherein W' may include 0, 1, or 2 =O groups when W' is a C_3-C_{10} cycloalkyl or a 3-10 membered heterocyclyl, and further wherein the =O groups may be bonded to a ring carbon atom or a ring S atom;

W" may be absent or is selected from a C_3-C_{10} cycloalkyl; a 3-10 membered heterocyclyl comprising 1, 2, or 3 heteroatoms selected from N, O, and S; a C_6-C_{10} aryl; or a 5-10 membered heteroaryl comprising 1, 2, 3, or 4 heteroatoms independently selected from N, O, or S; wherein the C_3-C_{10} cycloalkyl and the 3-10 membered heterocyclyl may be monocyclic or bicyclic, and further wherein the C_3-C_{10} cycloalkyl,

the 3-10 membered heterocyclyl, the C_6-C_{10} aryl, or the 5-10 membered heteroaryl W" groups are unsubstituted or are optionally substituted with 1, 2, 3, or 4 substituents independently selected from –F, -Cl, -Br, -I, -C≡N, -NO_2, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -OH, -NH_2, -NH((C_1-C_4)alkyl), -N((C_1-C_4)alkyl)$_2$, -CF_3, -CO_2H, -C(=O)-O-(C_1-C_4)alkyl, -SH, -S-(C_1-C_6)alkyl, -OCF_3, or -$OCHF_2$; and further wherein W" may include 0, 1, or 2 =O groups when W" is a C_3-C_{10} cycloalkyl or a 3-10 membered heterocyclyl, and further wherein the =O groups may be bonded to a ring carbon atom or a ring S atom;

the subscript q is, in each instance, independently selected from 0, 1, 2, 3, or 4;

R^a is, in each instance, independently selected from –H, -CH_3, -CH_2CH_3, -F, -CF_3, or -C≡N;

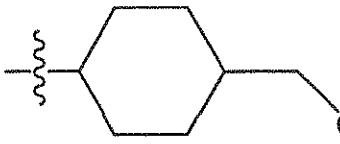
$R^{a'}$ is, in each instance, independently selected from –H, -CH_3, -CH_2CH_3, -F, -CF_3, or -C≡N; or R^a and $R^{a'}$ may join to form a cyclopropyl ring together with the carbon atom to which they are attached;

Z is selected from a C_6-C_{10} aryl; a 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S, or N; a 4-7 membered heterocyclyl comprising 1, 2, or 3 heteroatoms selected from O, S, or N; a C_3-C_7 cycloalkyl; a -N(H)-heterocyclyl, wherein the heterocyclyl of -N(H)-heterocyclyl is a 4-7 membered heterocyclyl comprising 1, 2, or 3 heteroatoms selected from O, S, or N; a-N(H)-(C_3-C_7)cycloalkyl; or Z is a –O-(C_1-C_6)alkyl; wherein the C_6-C_{10} aryl, the 5-10 membered heteroaryl, the 4-7 membered heterocyclyl, the C_3-C_7 cycloalkyl; the -N(H)-heterocyclyl, and the -N(H)-(C_3-C_7)cycloalkyl are unsubstituted or are optionally substituted with 1, 2, or 3 substituents independently selected from –F, -Cl, -Br, -I, -C≡N, -NO_2, -CF_3, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_1-C_4)alkylene-OH, -NH_2, -NH((C_1-C_6)alkyl), -N((C_1-C_6)alkyl)$_2$, -C(=O)NH_2, -C(=O)NH((C_1-C_6)alkyl), -C(=O)N((C_1-C_6)alkyl)$_2$, -SO_2NH_2, -SO_2NH((C_1-C_6)alkyl), -SO_2N((C_1-C_6)alkyl)$_2$, -SO_2NH((C_2-C_6)alkenyl), -SO_2NH((C_2-C_6)alkynyl), -SO_2NH-(C_1-C_4)alkylene-OH, -SO_2NH-(C_1-C_4)alkylene-O-(C_1-C_6)alkyl, -NHSO_2-(C_1-C_6)alkyl, -NHC(=O)-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO-(C_1-C_6)alkyl, -(C_1-C_4)alkylene-NH-C(=O)-(C_1-C_6)alkyl, -C(=O)-(C_1-C_6)alkyl, -CO_2H, -C(=O)-O-(C_1-C_6)alkyl, -C(=O)NH-(C_1-C_4)alkylene-NH_2, -C(=O)NH-(C_1-C_4)alkylene-NH((C_1-C_6)alkyl), -C(=O)NH-(C_1-C_4)alkylene-N((C_1-C_6)alkyl)$_2$, -(C_1-C_4)alkylene-C(=O)-(C_1-C_6)alkyl, -(C_1-C_4)alkylene-C(=O)-O-(C_1-C_6)alkyl, -(C_1-C_4)alkylene-C(=O)-OH, -OH, -O-(C_1-C_6)alkyl, -SH, -S-(C_1-C_6)alkyl, -OCF_3, or -$OCHF_2$;

W is not –H, -F, -Cl, -Br, -I, or unsubstituted -(C_1-C_6)alkyl if X is CR^4;

Y is not unsubstituted cyclopropyl, cyclobutyl, or cyclopentyl if W is -H, -F, -Cl, -Br, -I, or -(C_1-C_6)alkyl;

W is not –CH_2OH or –CH_2O(C_1-C_4alkyl) if Y is a group of formula



; and

W is not –SH, -OH, –S-(C_1-C_6)alkyl), or –S-(C_1-C_6)alkyl) if Z is –O-(C_1-C_6)alkyl);

wherein the symbol ∿∿∿, when drawn across a bond, indicates the point of attachment to the rest of the molecule.

2. The compound of Claim 1, wherein X is N, or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, a stereoisomer of any of the foregoing, or a mixture thereof.

3. The compound of Claim, wherein X is CR^4, or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, a stereoisomer of any of the foregoing, or a mixture thereof.

4. The compound of Claims 3, wherein R^4 is –H, or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, a stereoisomer of any of the foregoing, or a mixture thereof.

5. The compound of any one of Claims 1-4, wherein R^3 is –H, or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, a stereoisomer of any of the foregoing, or a mixture thereof.

6. The compound of any one of Claims 1-5, wherein Z is selected from -OMe or -NH-cyclohexyl; or an unsubstituted or substituted phenyl, pyridyl, benzothiophenyl, thiazolyl, pyradizinyl, pyrimidinyl, indolyl, cyclohexyl, morpholinyl, pyrrolidinyl, piperazinyl, or piperidinyl group, or a pharmaceutically acceptable salt

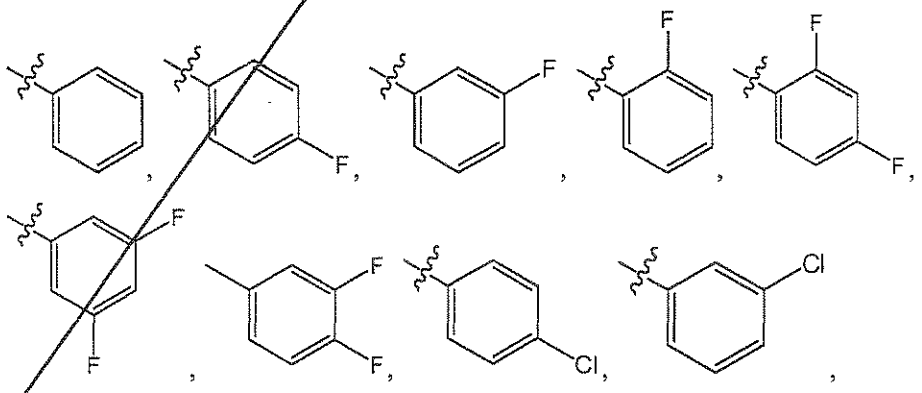
thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, a stereoisomer of any of the foregoing, or a mixture thereof.

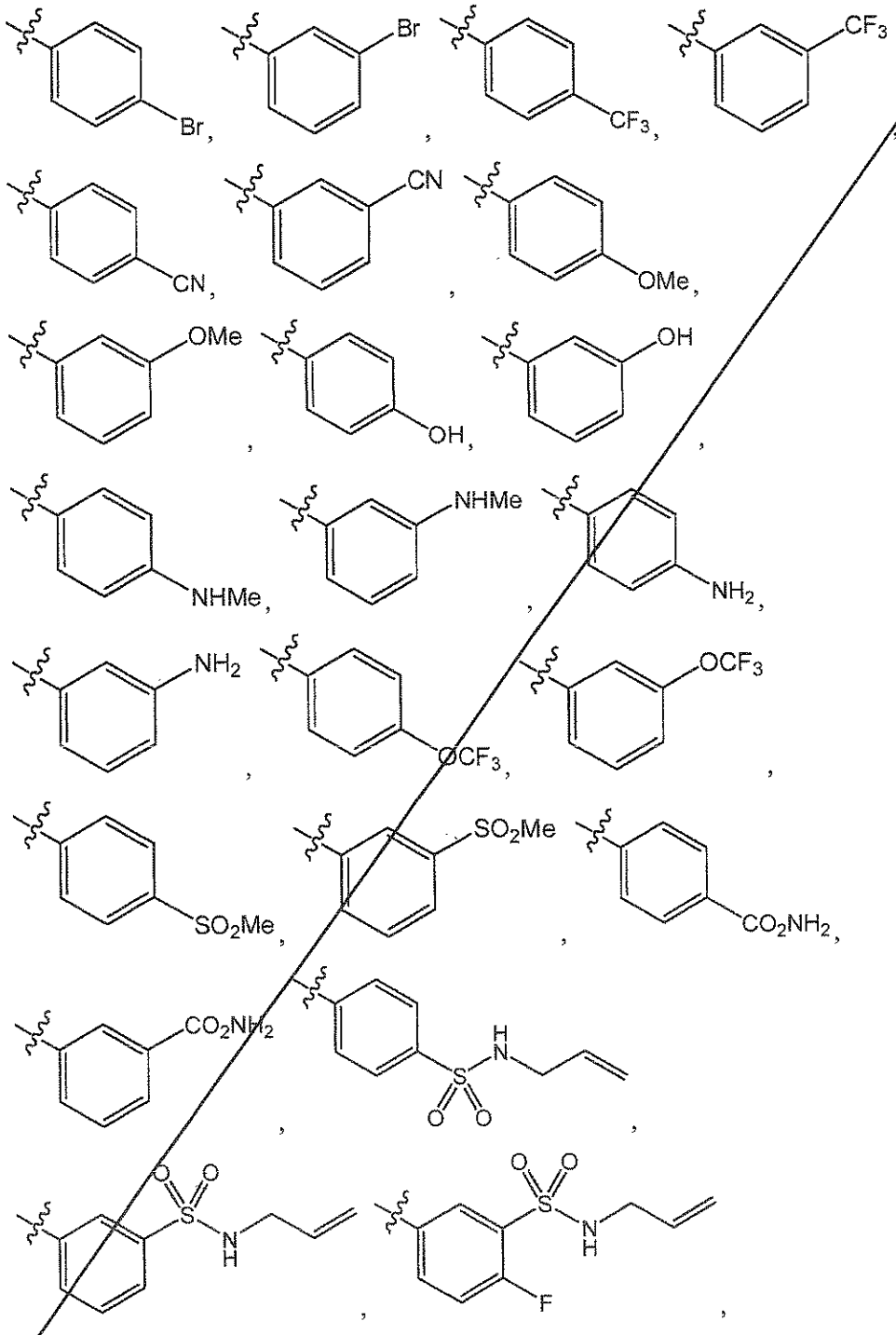
7. The compound of any one of Claims 1-5, wherein Z is an unsubstituted or substituted phenyl, pyridyl, benzothiophenyl, thiazolyl, pyradizinyl, pyrimidinyl, indolyl, cyclohexyl, morpholinyl, pyrrolidinyl, piperazinyl, piperidinyl, isothiazolyl, or thiomorpholinyl group, or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, a stereoisomer of any of the foregoing, or a mixture thereof.

8. The compound of Claim 6, wherein Z is an unsubstituted or substituted phenyl, pyridyl, benzothiophenyl, thiazolyl, pyradizinyl, pyrimidinyl, indolyl, cyclohexyl, morpholinyl, pyrrolidinyl, piperazinyl, or piperidinyl group, or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, a stereoisomer of any of the foregoing, or a mixture thereof.

9. The compound of Claim 6, wherein Z is an unsubstituted or substituted phenyl or pyridyl, or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, a stereoisomer of any of the foregoing, or a mixture thereof.

10. The compound of any one of Claims 1-5, wherein Z is selected from




Br
Br
CF3
CF3
CN
CN
OMe
OMe
OH
OH
NHMe
NHMe
NH2
NH2
OCF3
OCF3
SO2Me
SO2Me
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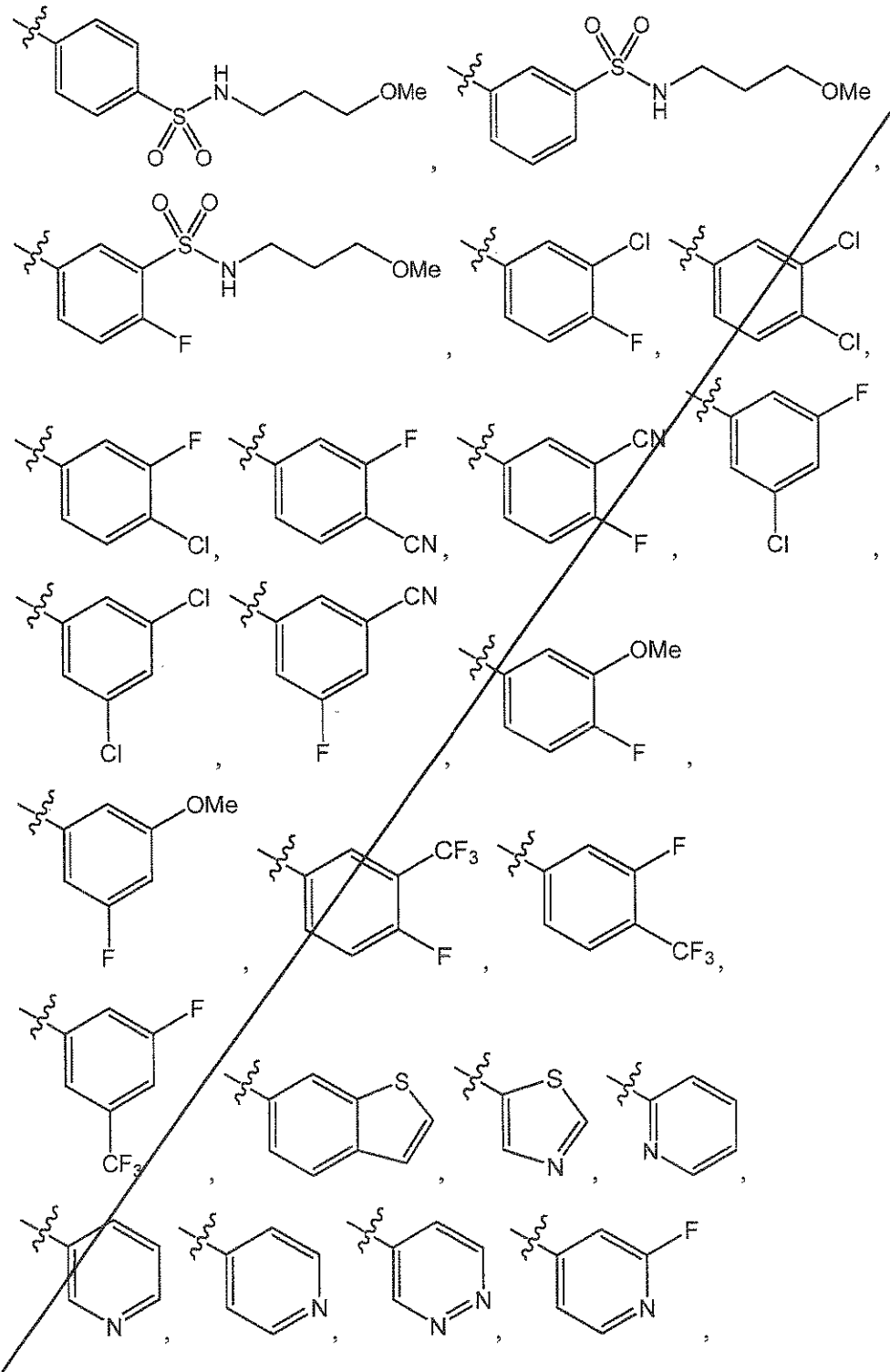
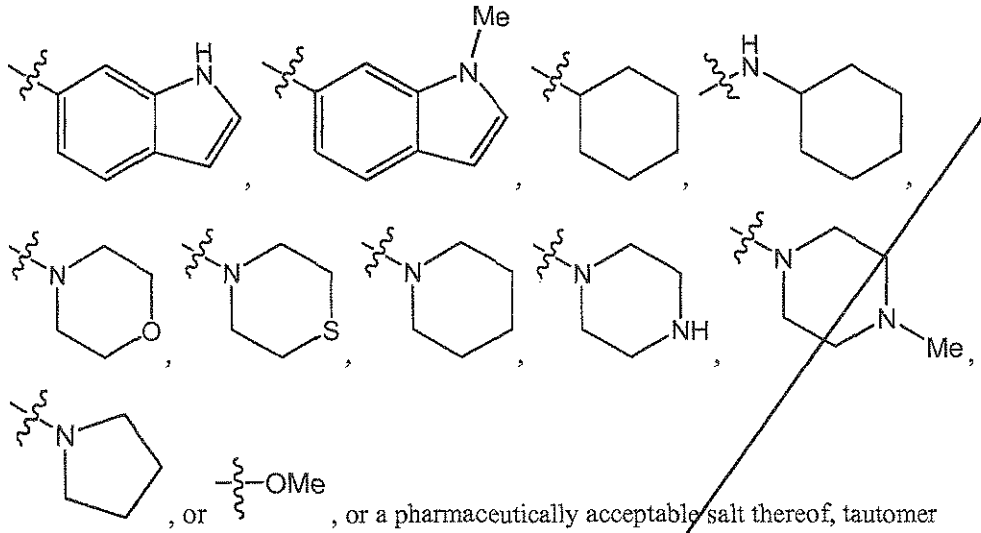
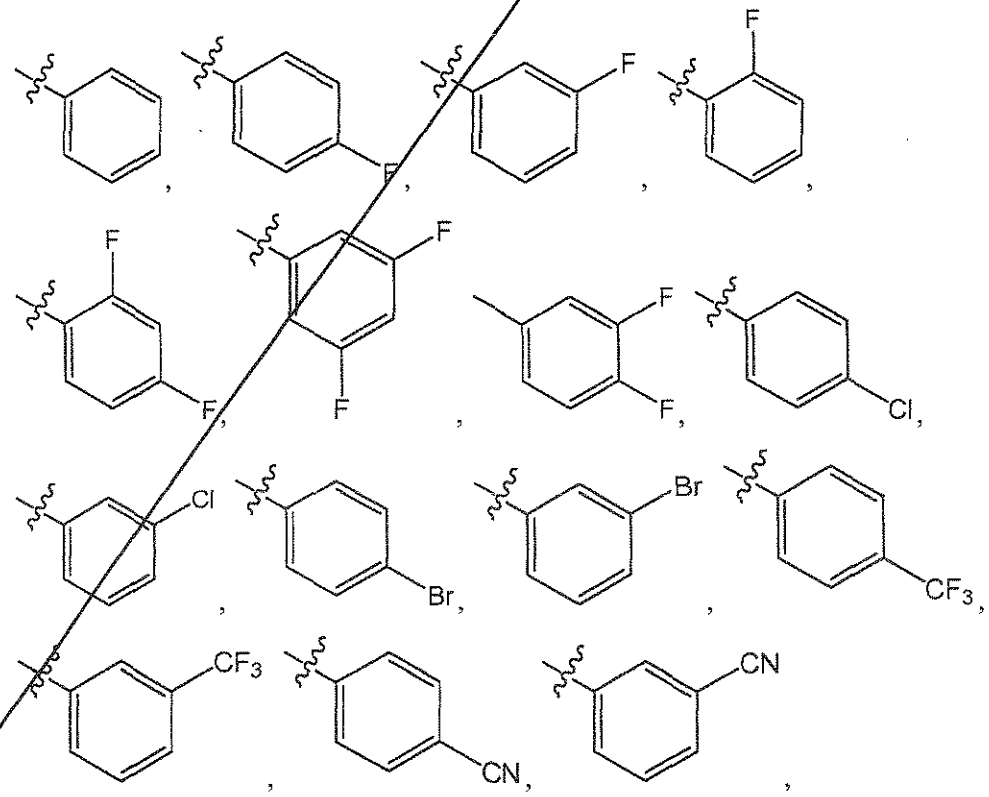
O
O
S
N
H
F

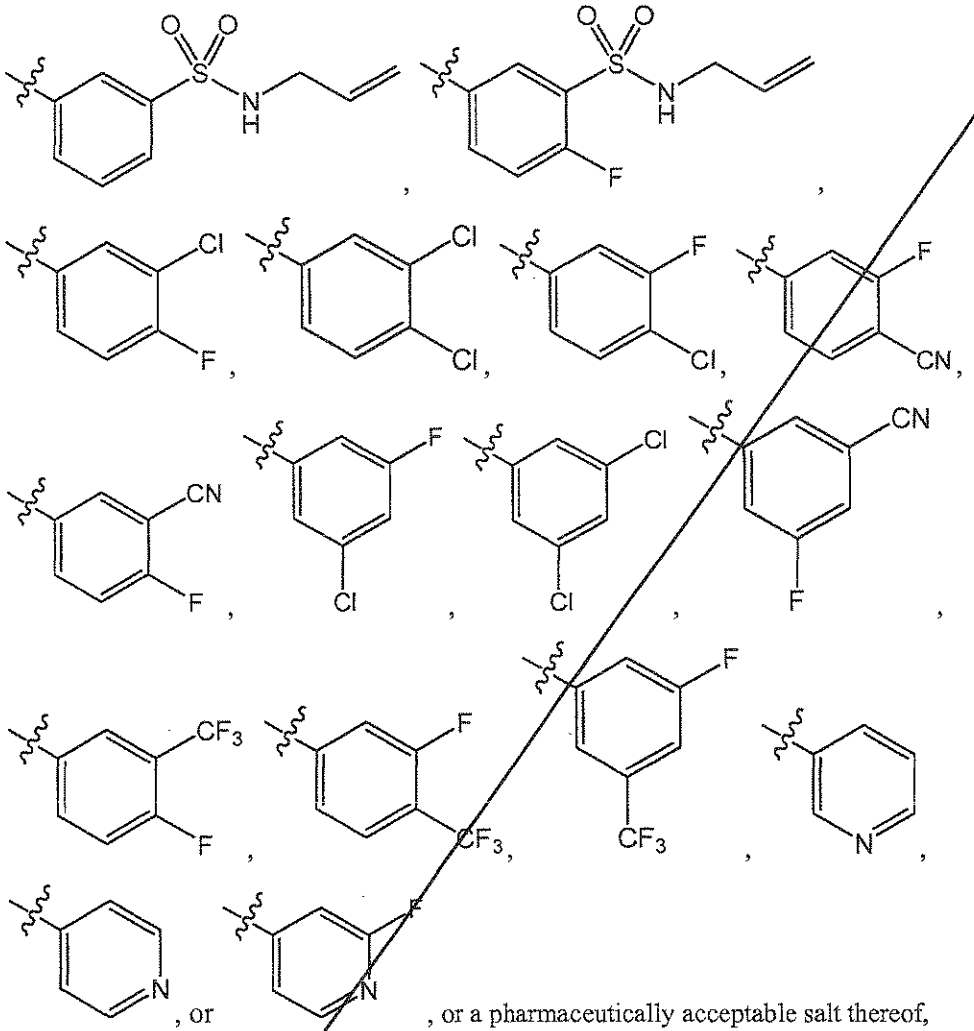




, or , or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, a stereoisomer of any of the foregoing, or a mixture thereof, wherein the symbol , when drawn across a bond, indicates the point of attachment to the rest of the molecule.

11. The compound of any one of Claims 1-5, wherein Z is selected from





, or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, a stereoisomer of any of the foregoing, or a mixture thereof, wherein the symbol ~~~, when drawn across a bond, indicates the point of attachment to the rest of the molecule.

12. The compound of any one of Claims 1-11, wherein Y is an unsubstituted or substituted cycloheptyl, cyclohexyl, cyclopentyl, cyclobutyl, piperidinyl, pyrrolidinyl, azetidinyl, adamantyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[4.1.1]octyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, or bicyclo[2.1.1]hexyl, or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, a stereoisomer of any of the foregoing, or a mixture thereof.

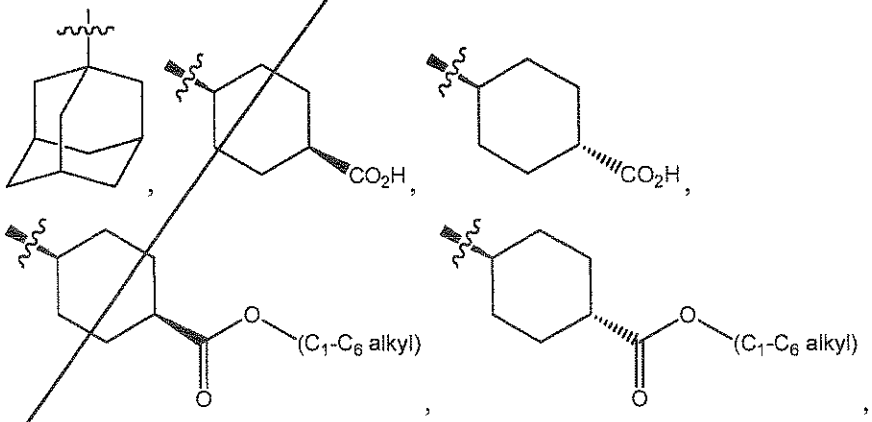
13. The compound of Claim 12, wherein Y is an unsubstituted or substituted cyclohexyl, or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, a stereoisomer of any of the foregoing, or a mixture thereof.

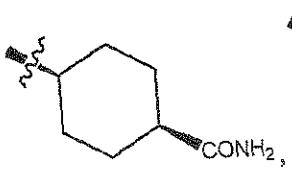
14. The compound of Claim 12, wherein Y is an unsubstituted or substituted adamantyl, or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, a stereoisomer of any of the foregoing, or a mixture thereof.

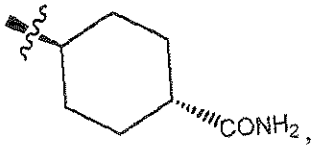
15. The compound of Claim 12, wherein Y is an unsubstituted or substituted cyclobutyl, or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, a stereoisomer of any of the foregoing, or a mixture thereof.

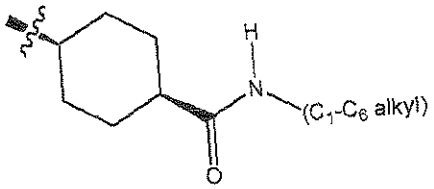
16. The compound of Claim 12, wherein Y is an unsubstituted or substituted piperidinyl, or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, a stereoisomer of any of the foregoing, or a mixture thereof.

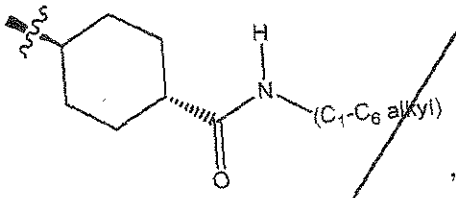
17. The compound of any one of Claims 1-11, wherein Y is selected from

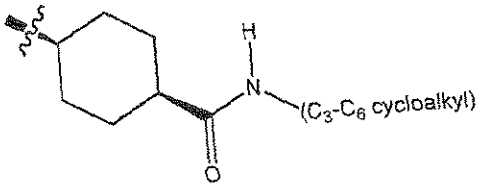


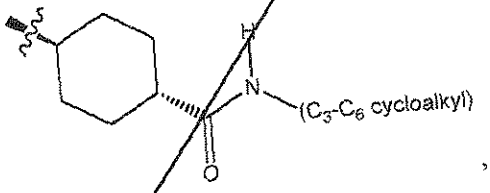

CONH2

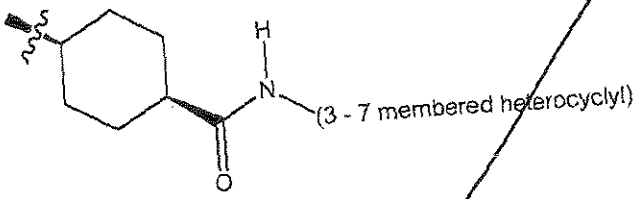

CONH2

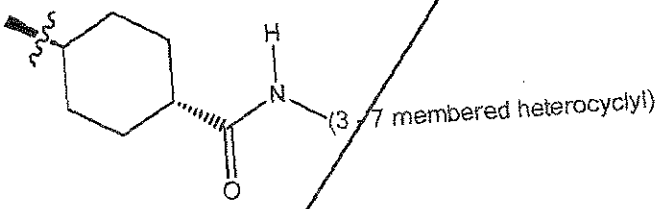

H
N
(C1-C6 alkyl)
O

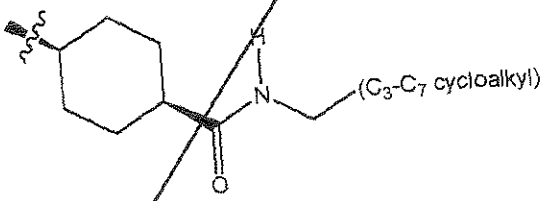

H
N
(C1-C6 alkyl)
O

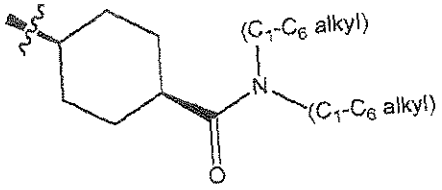

H
N
(C3-C6 cycloalkyl)
O

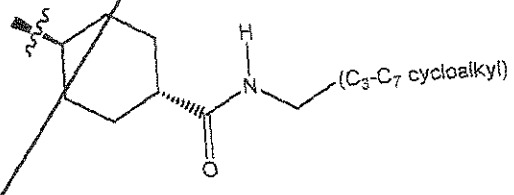

H
N
(C3-C6 cycloalkyl)
O

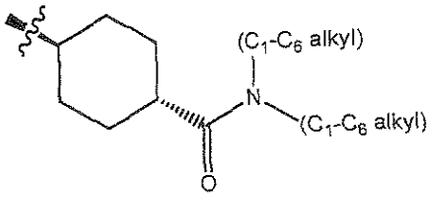

H
N
(3 - 7 membered heterocyclyl)
O


H
N
(3 - 7 membered heterocyclyl)
O

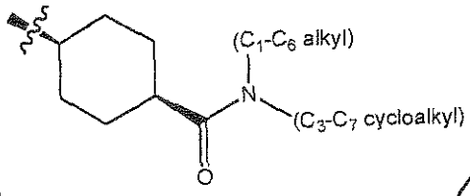

H
N
(C3-C7 cycloalkyl)
O


(C1-C6 alkyl)
N
(C1-C6 alkyl)
O

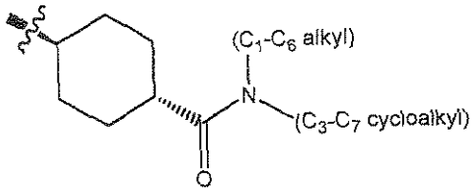

H
N
(C3-C7 cycloalkyl)
O


(C1-C6 alkyl)
N
(C1-C6 alkyl)
O

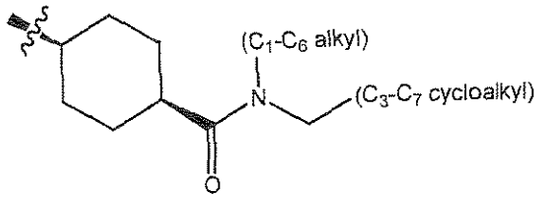
,


(C1-C6 alkyl)
N
(C3-C7 cycloalkyl)
O

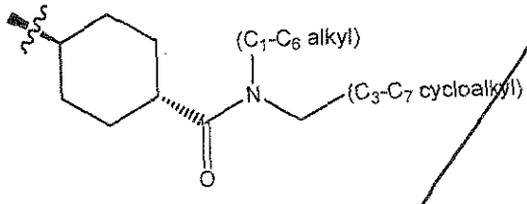
,


(C1-C6 alkyl)
N
(C3-C7 cycloalkyl)
O

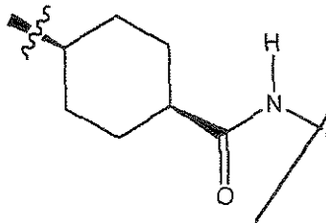
,


(C1-C6 alkyl)
N
(C3-C7 cycloalkyl)
O

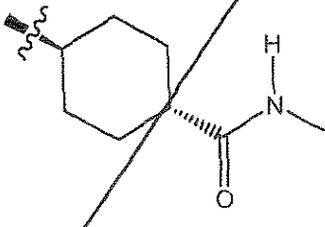
,


(C1-C6 alkyl)
N
(C3-C7 cycloalkyl)
O

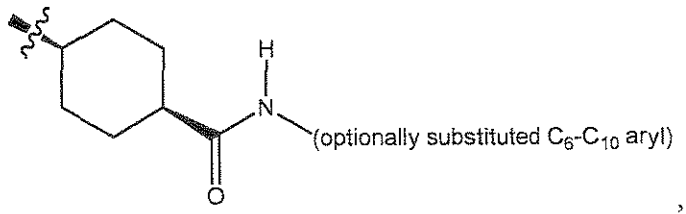
,

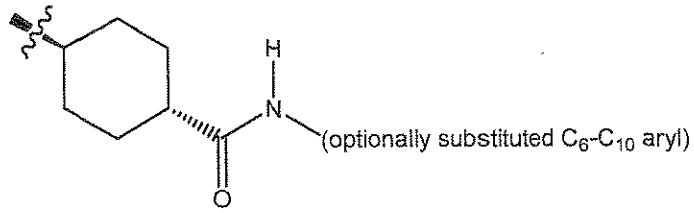

H
N
(optionally substituted 5 - 10 membered heteroaryl)
O

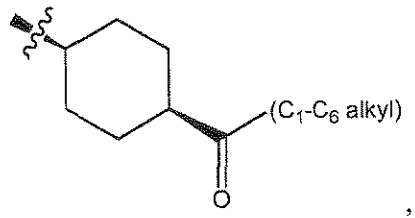
,

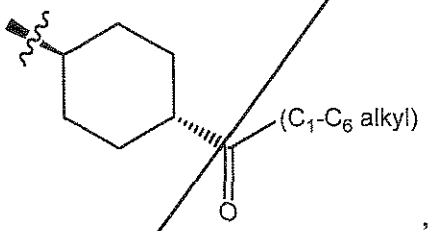

H
N
(optionally substituted 5 - 10 membered heteroaryl)
O

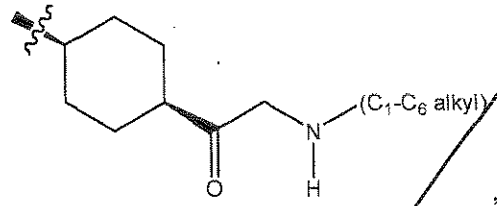
,

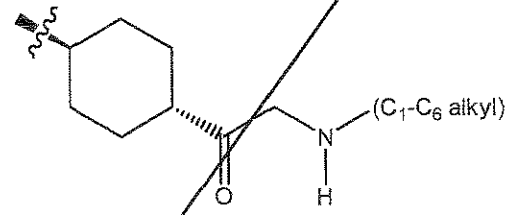

H
N
(optionally substituted C_6-C_{10} aryl)
O

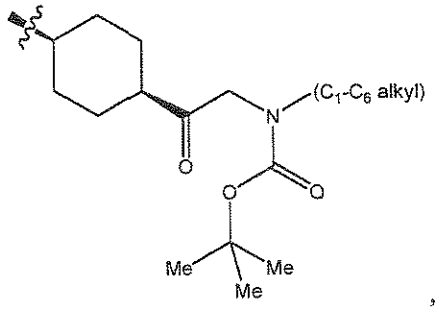

H
N
(optionally substituted C_6-C_{10} aryl)
O

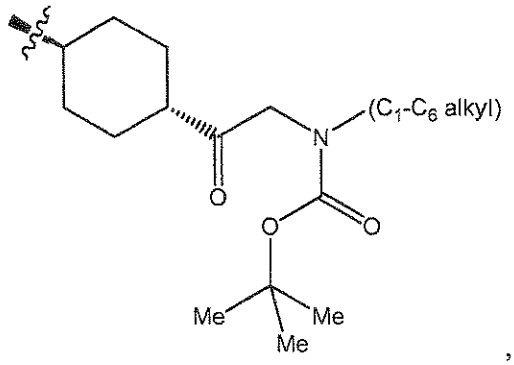

(C_1-C_6 alkyl)
O


(C_1-C_6 alkyl)
O

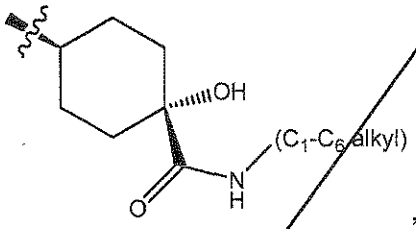

(C_1-C_6 alkyl)
N
H
O


(C_1-C_6 alkyl)
N
H
O

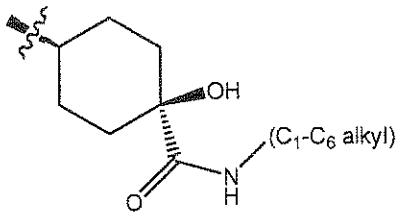

(C_1-C_6 alkyl)
N
O
O
O
Me
Me
Me


(C1-C6 alkyl)
N
O
O
O
Me
Me
Me

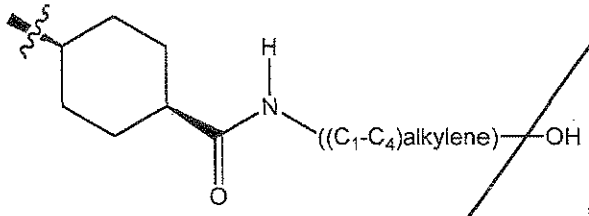
,


OH
(C1-C6 alkyl)
N
H
O

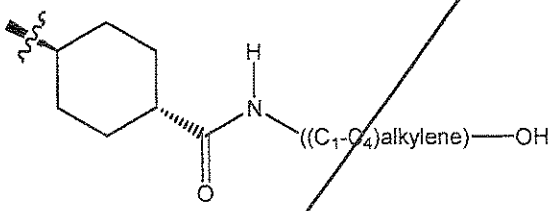
,


OH
(C1-C6 alkyl)
N
H
O

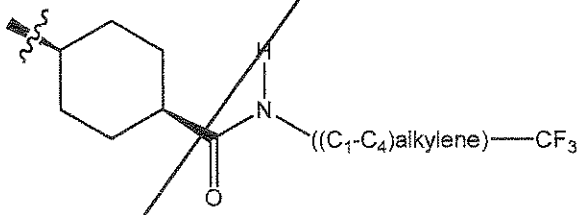
,


H
N
((C1-C4)alkylene)—OH
O

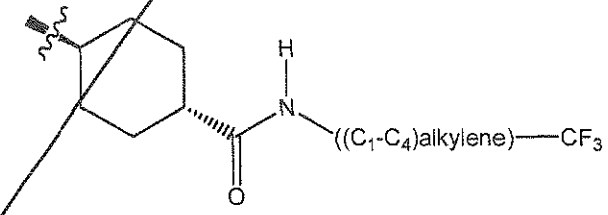
,


H
N
((C1-C4)alkylene)—OH
O

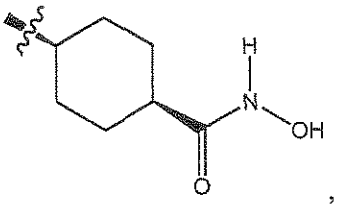
,


H
N
((C1-C4)alkylene)—CF3
O

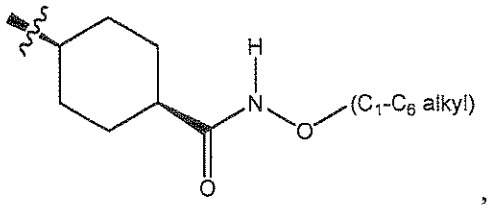
,

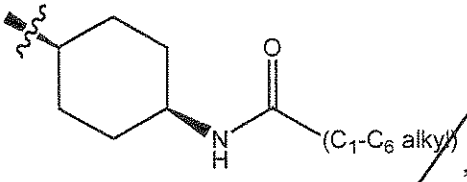

H
N
((C1-C4)alkylene)—CF3
O

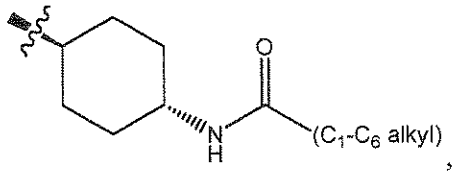
,

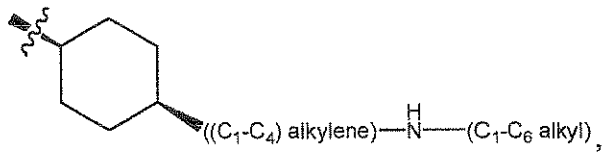

H
N
OH
O

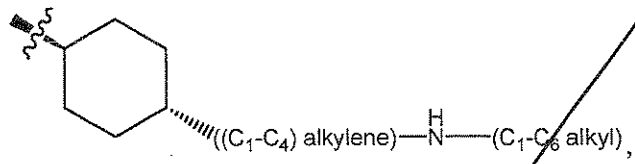
,

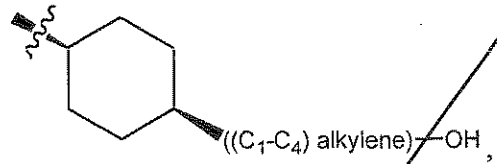

H
N
O
(C1-C6 alkyl)
O
,

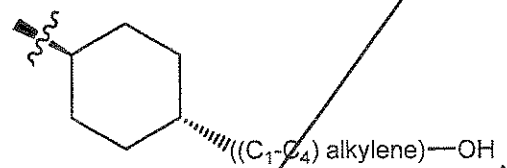

O
N
H
(C1-C6 alkyl)
,

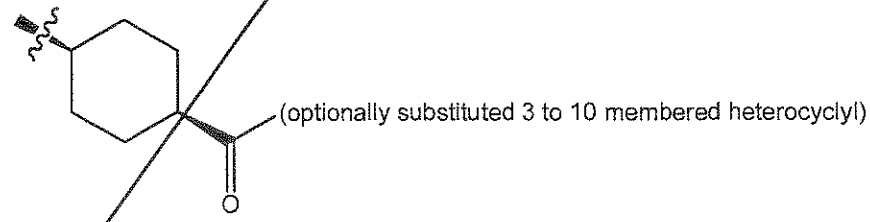

O
N
H
(C1-C6 alkyl)
,

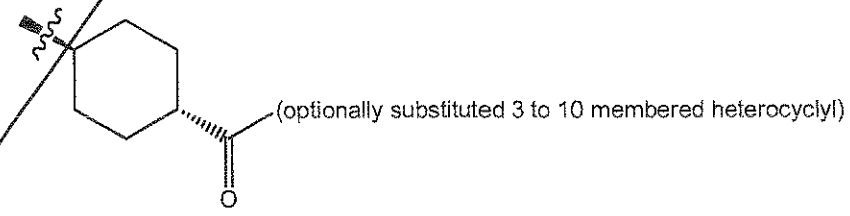

((C1-C4) alkylene)—N—(C1-C6 alkyl)
H
,

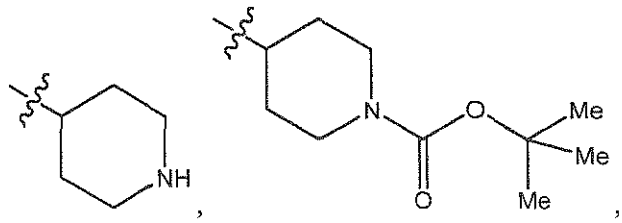

((C1-C4) alkylene)—N—(C1-C6 alkyl)
H
,


((C1-C4) alkylene)—OH
,

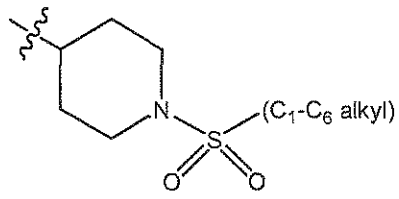

((C1-C4) alkylene)—OH
,


(optionally substituted 3 to 10 membered heterocyclyl)
O
,

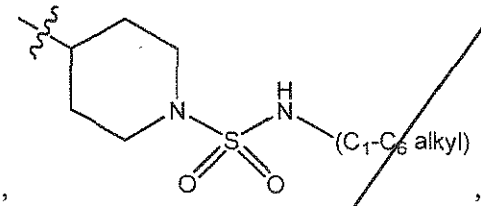

(optionally substituted 3 to 10 membered heterocyclyl)
O
,


NH
N
O
O
Me
Me
Me

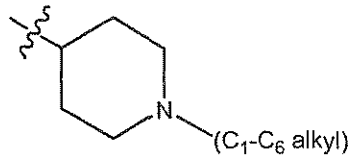
,


N
S
O
O
(C1-C6 alkyl)

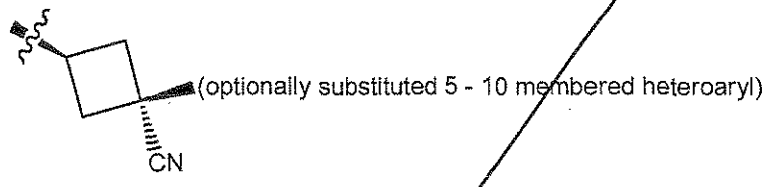
,


N
H
N
S
O
O
(C1-C6 alkyl)

,


N
(C1-C6 alkyl)

,


(optionally substituted 5 - 10 membered heteroaryl)
CN

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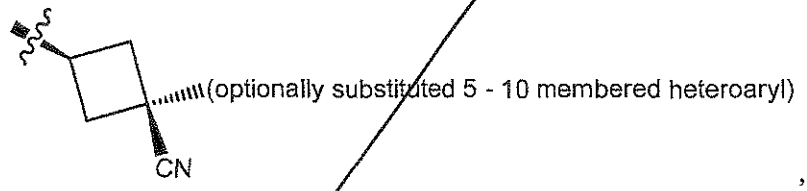
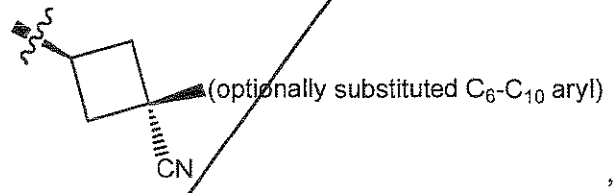

(optionally substituted 5 - 10 membered heteroaryl)
CN

,


(optionally substituted C6-C10 aryl)
CN

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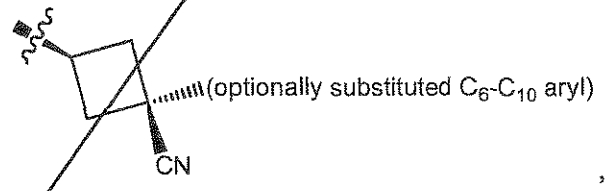
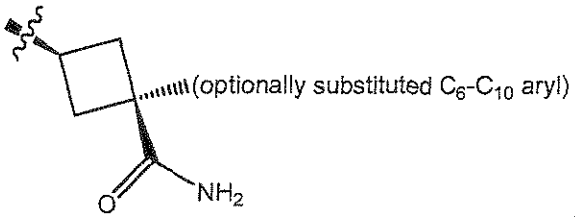

(optionally substituted C6-C10 aryl)
CN

,



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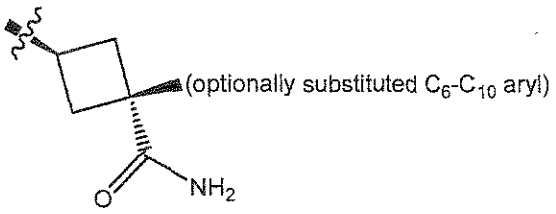
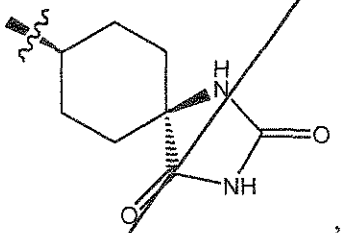


, or



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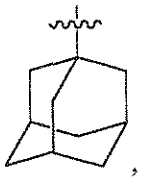
or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, a stereoisomer of any of the foregoing, or a mixture thereof, wherein the symbol ∿∿∿, when drawn across a bond, indicates the point of attachment to the rest of the molecule.

18. The compound any one of Claims 1-11, wherein Y is selected from



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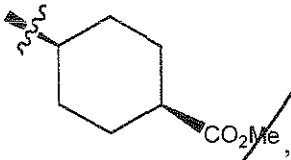

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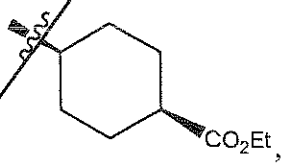

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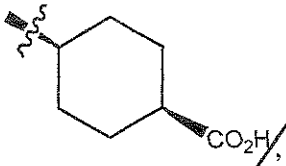

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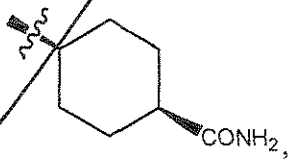

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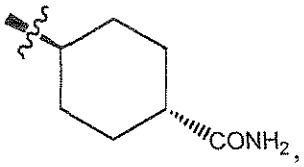

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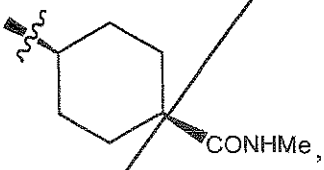

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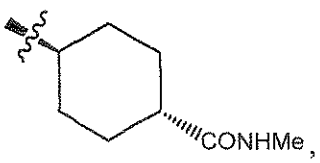

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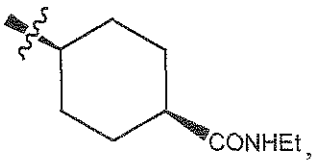

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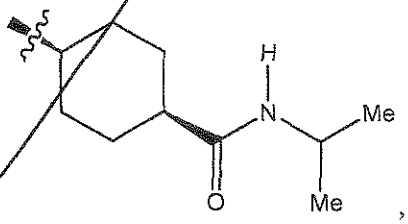

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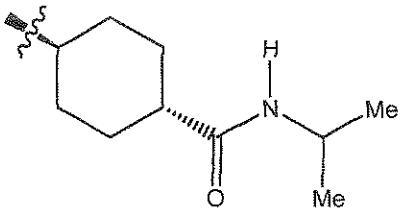

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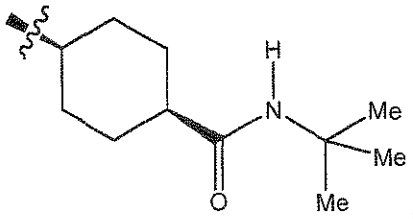
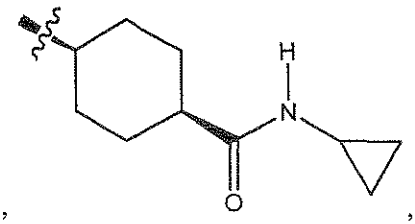
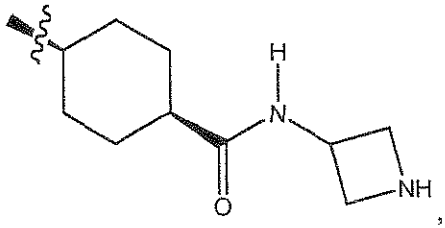
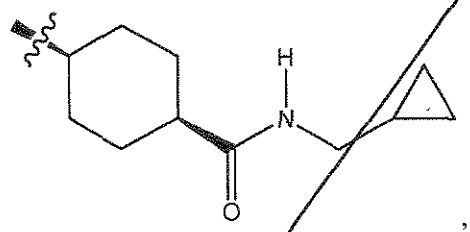
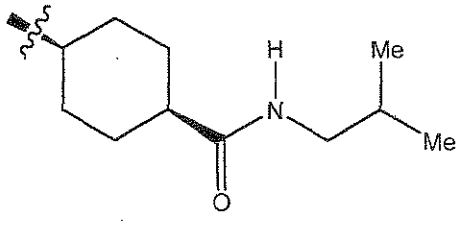
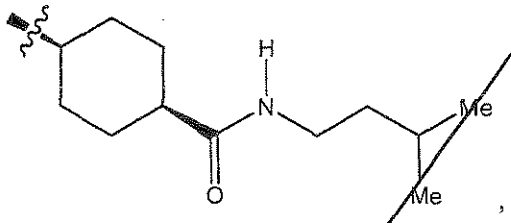
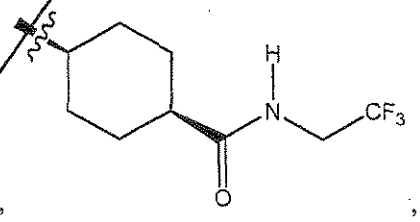
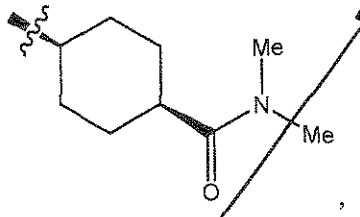
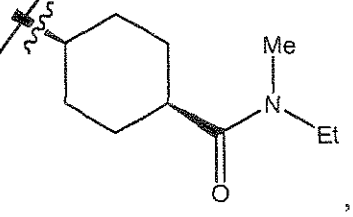
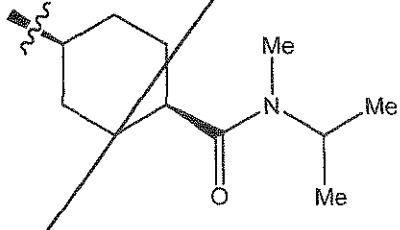
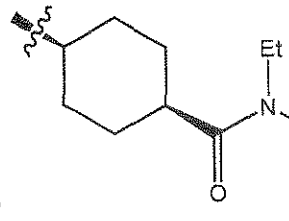

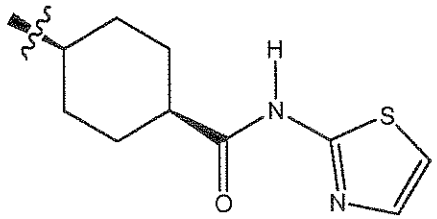
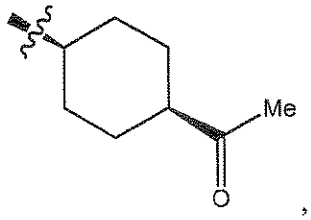
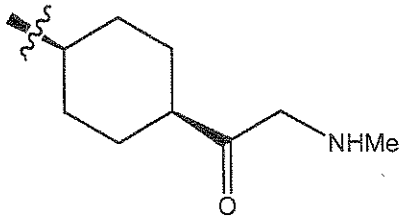
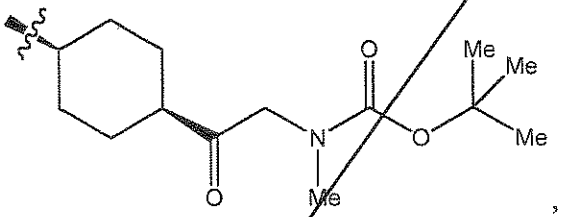
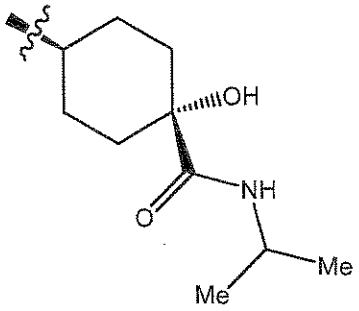
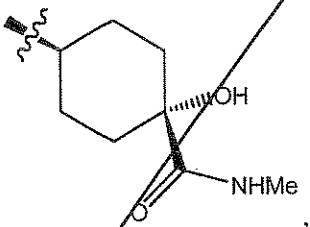
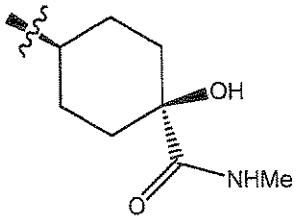
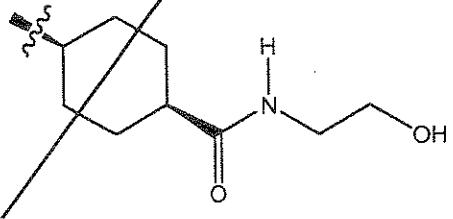
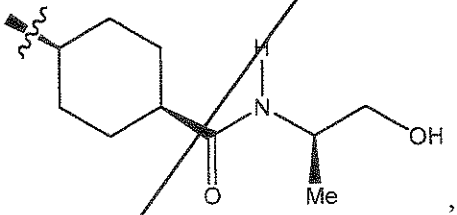
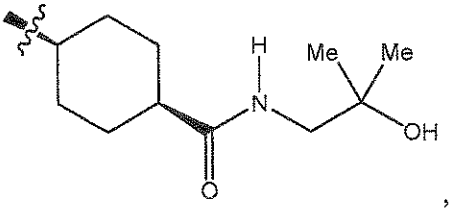
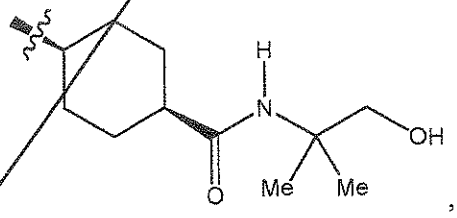
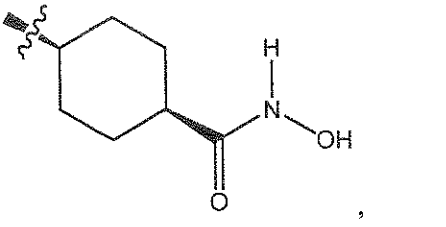

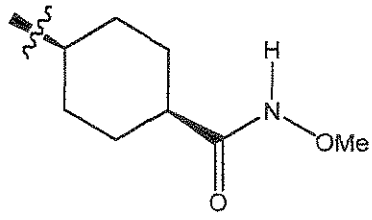
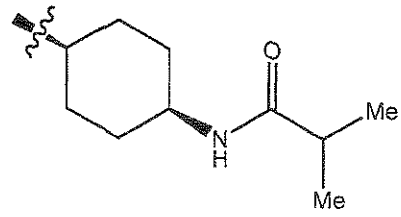
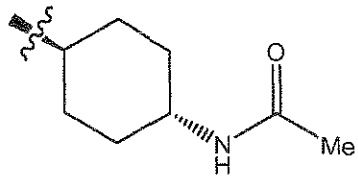
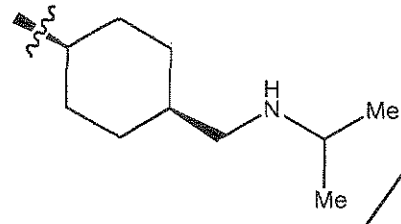
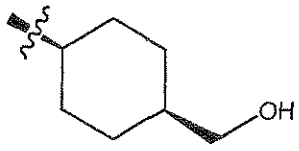
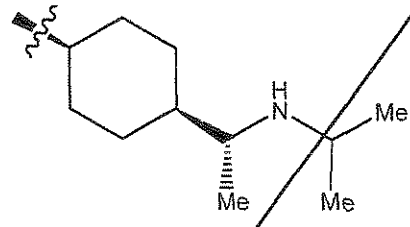
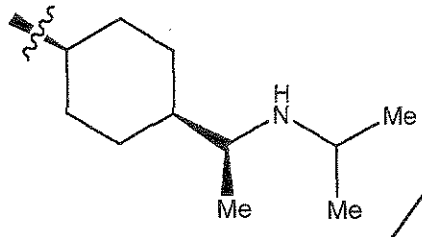
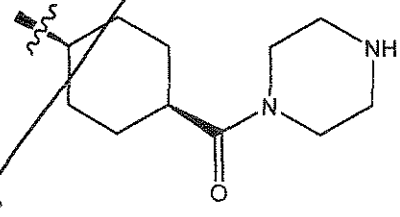
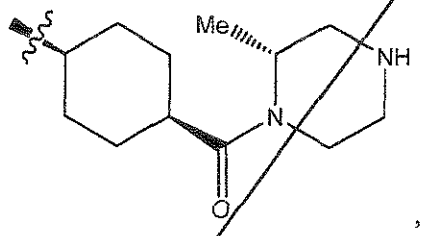

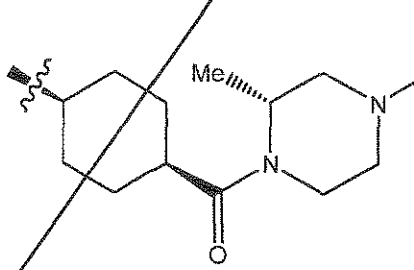

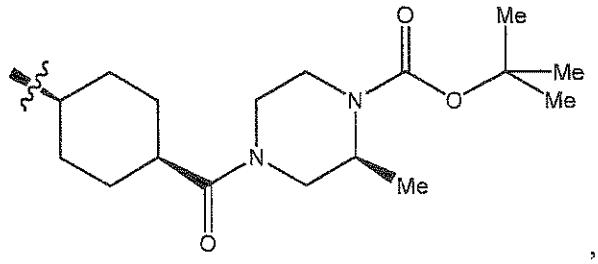

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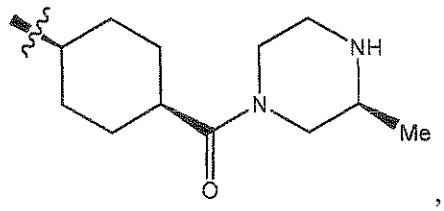

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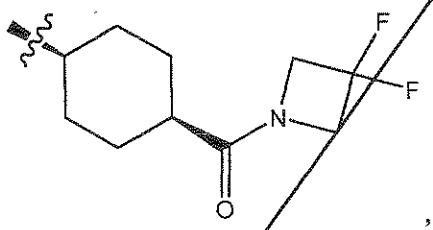

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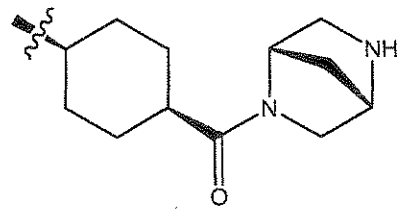

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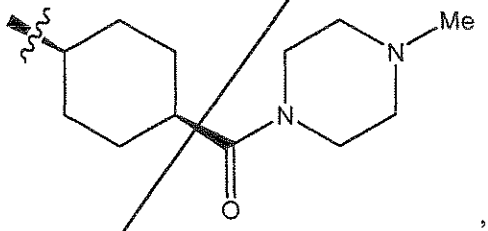

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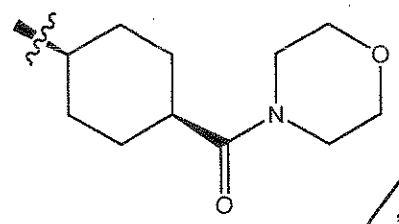

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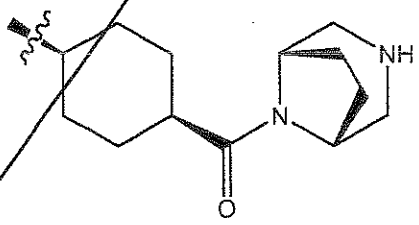

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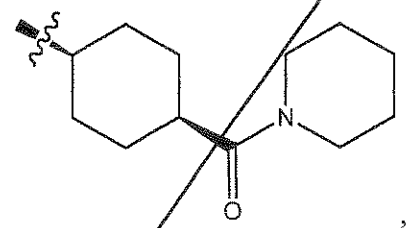

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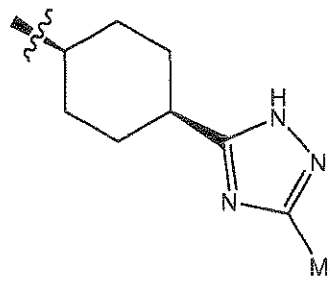

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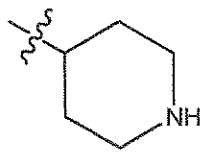

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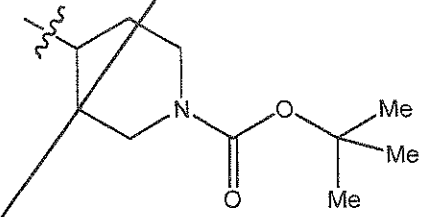

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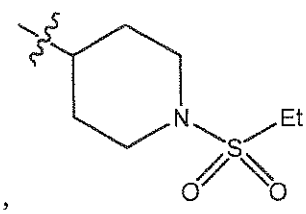

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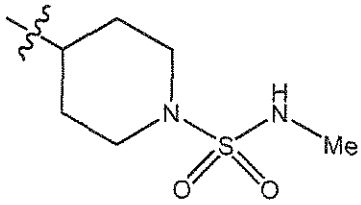
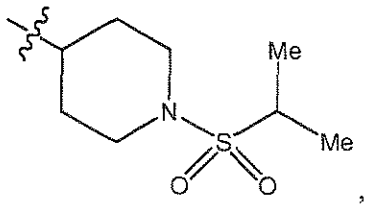
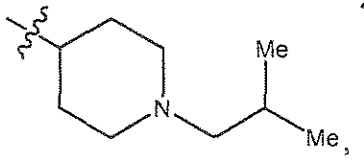
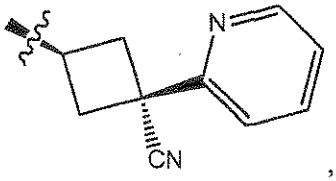
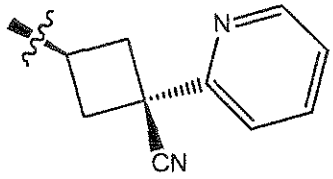
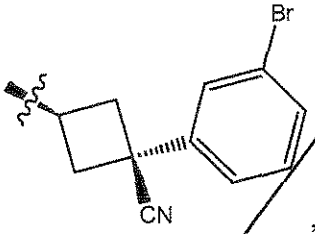
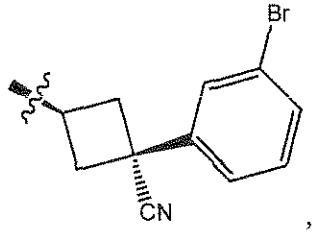
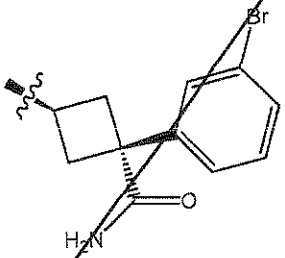
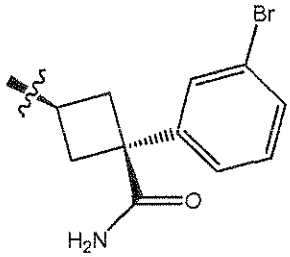
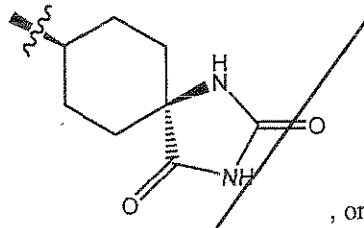
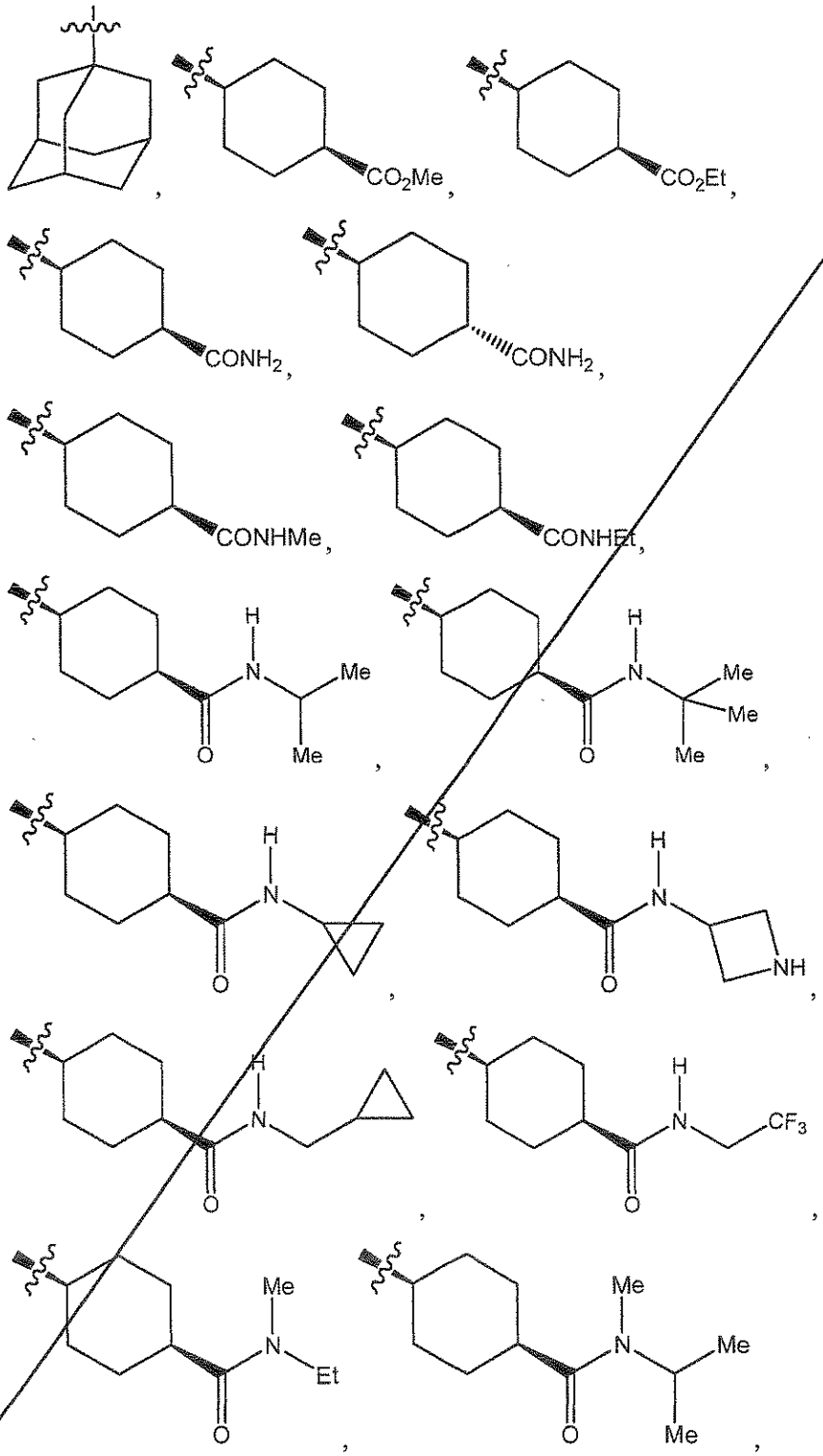









 , or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, a stereoisomer of any of the foregoing, or a mixture thereof, wherein the symbol ~~~, when drawn across a bond, indicates the point of attachment to the rest of the molecule.

19. The compound any one of Claims 1-11, wherein Y is selected from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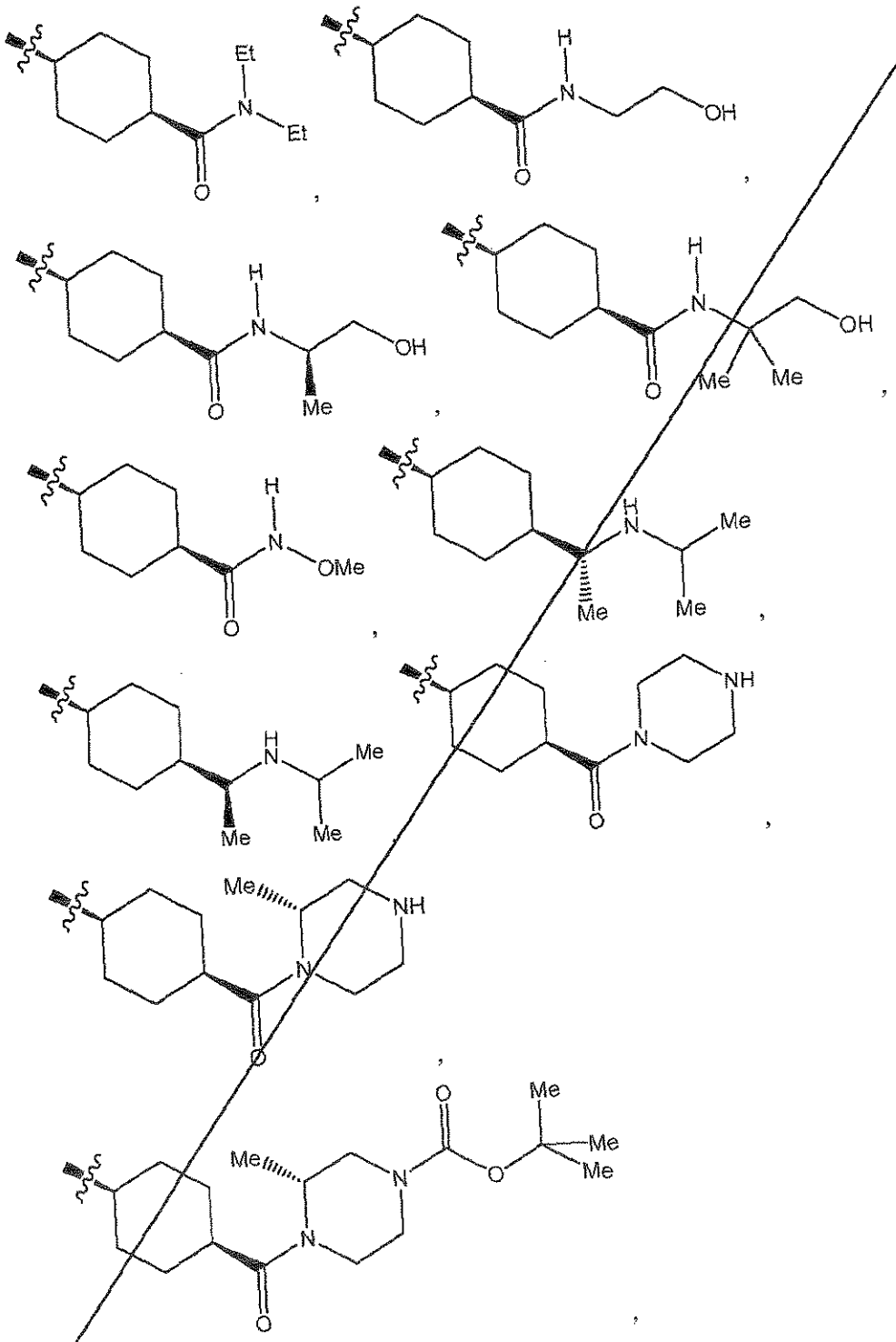

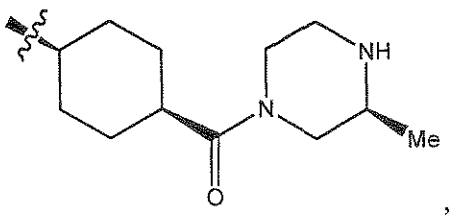

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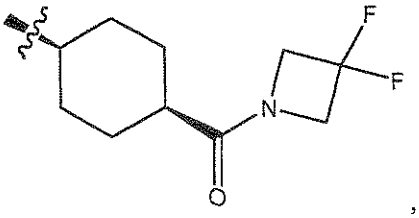

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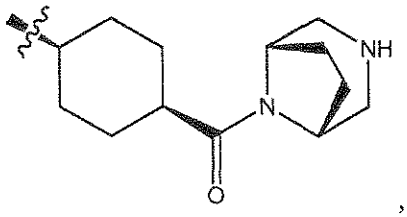

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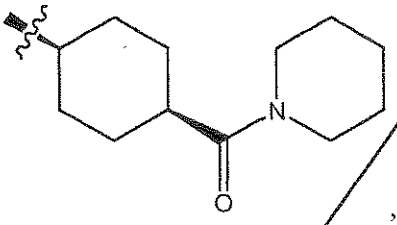

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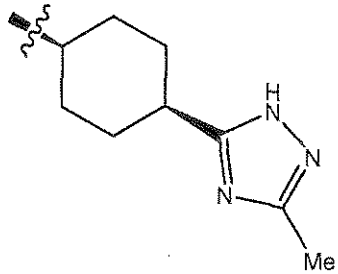
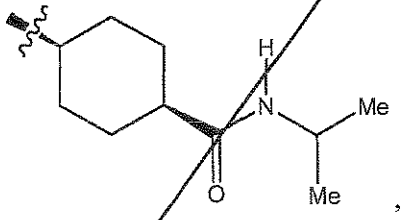


, or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, a stereoisomer of any of the foregoing, or a mixture thereof, wherein the symbol ∿∿∿, when drawn across a bond, indicates the point of attachment to the rest of the molecule.

20. The compound of claim 19, wherein Y is

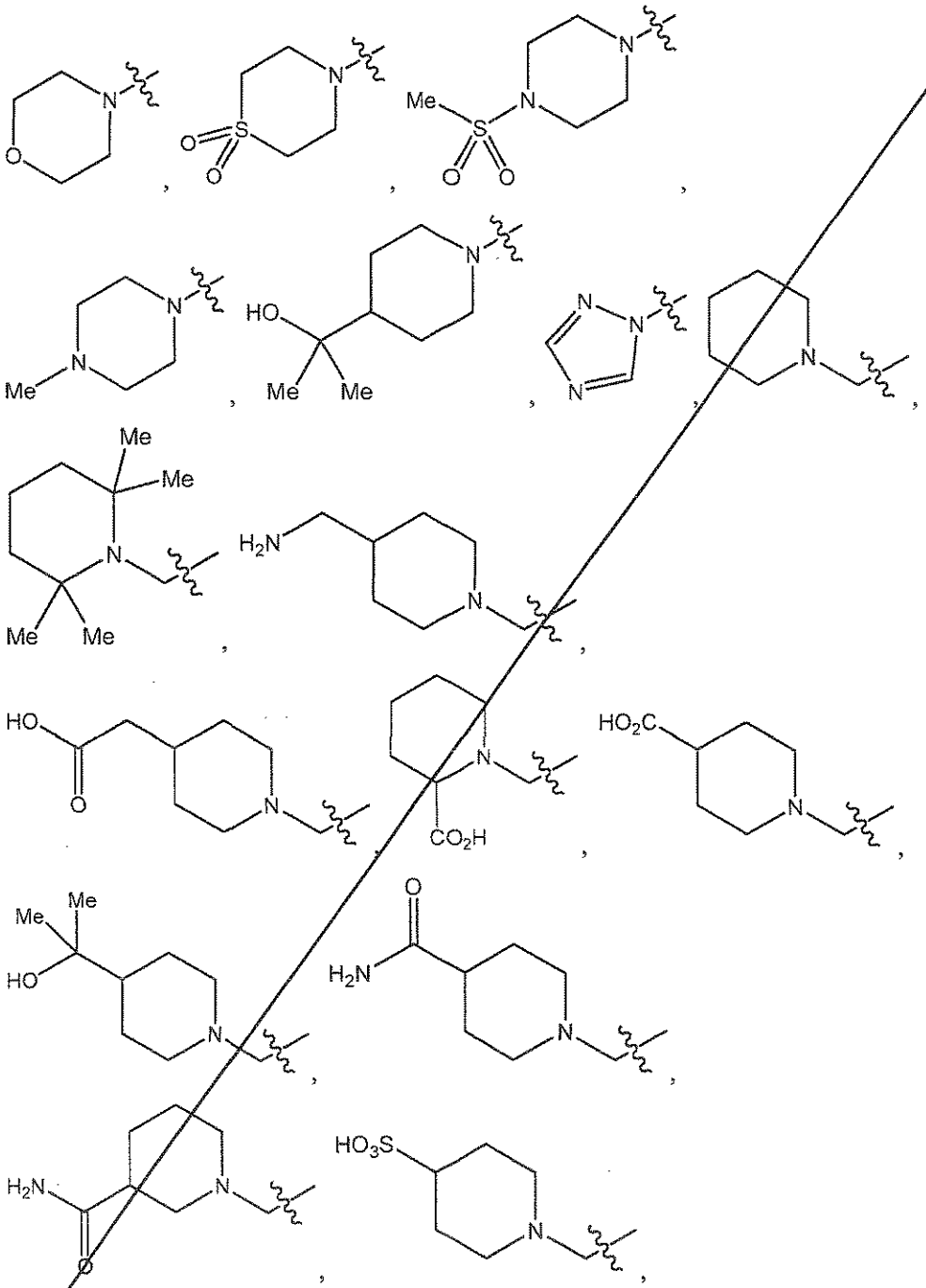


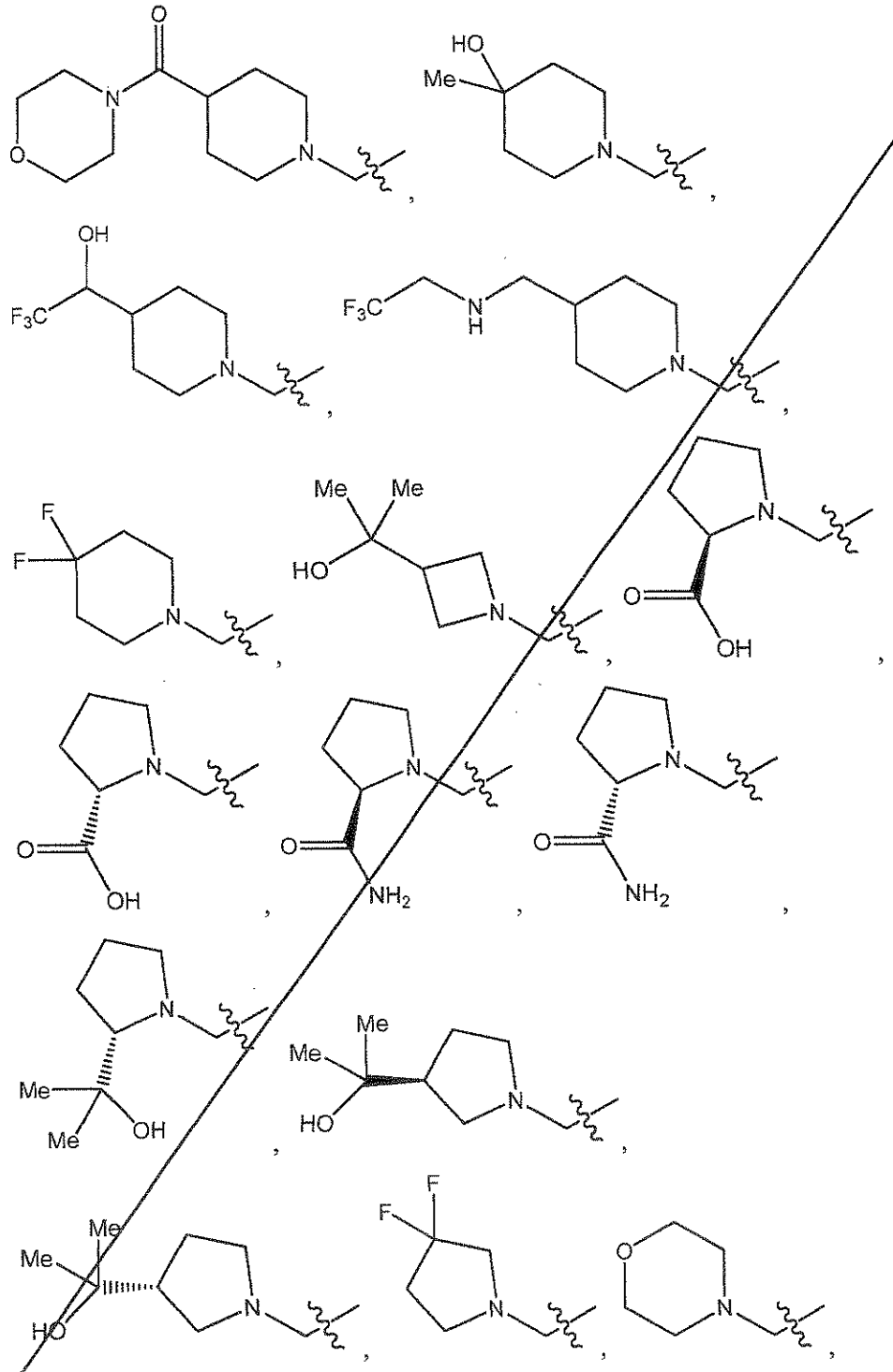
, or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, a stereoisomer of any of the foregoing, or a mixture thereof, wherein the symbol ∿∿∿, when drawn across a bond, indicates the point of attachment to the rest of the molecule.

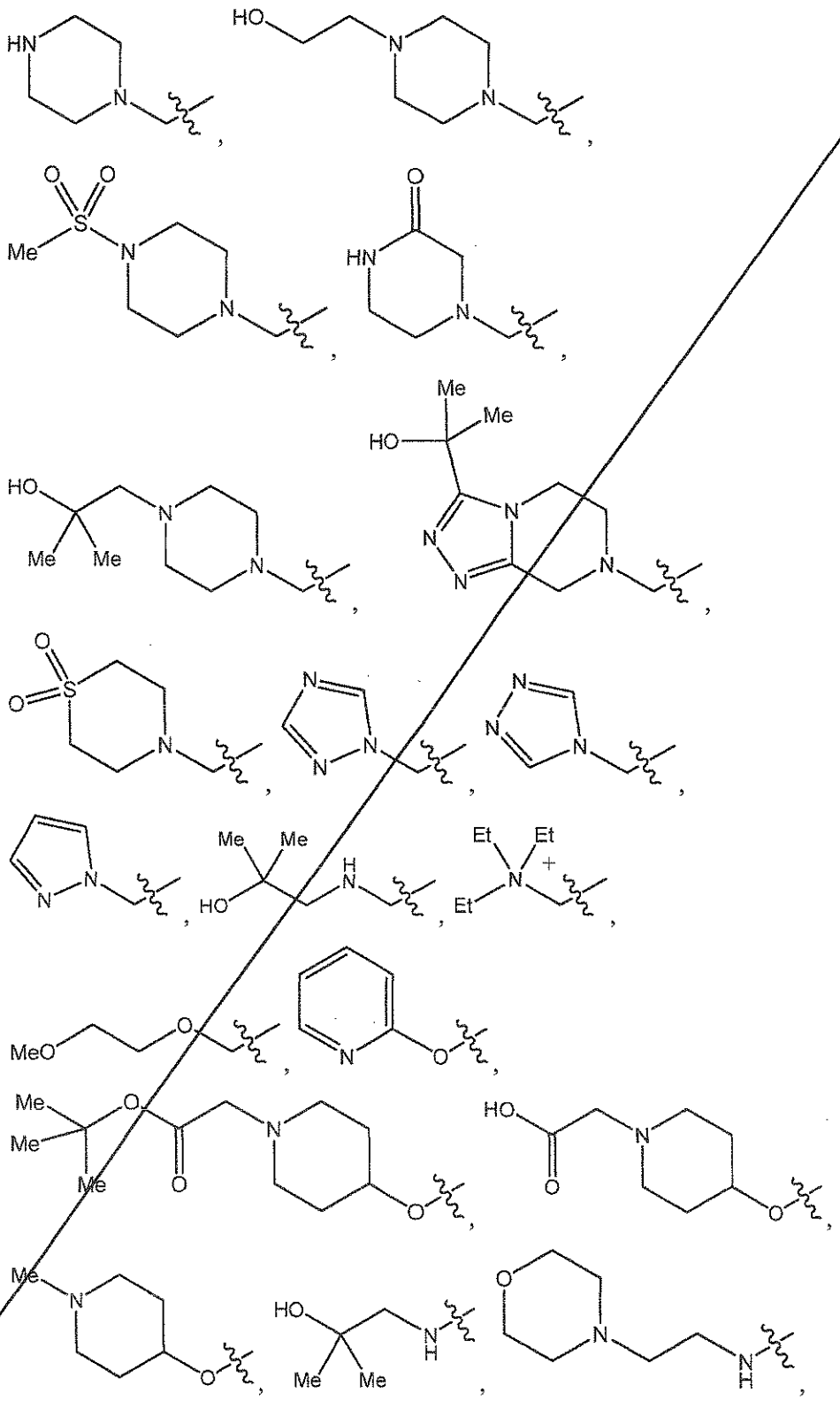
21. The compound of any one of Claims 1-20, wherein W is selected from $-CH_2OH$, $-CH_2OCH_3$, $-CH_2OCH_2CH_2OH$, $-CH_2OCH_2CH_2OCH_3$, $-OCH_2CH_2OH$, $-OCH_2CH_2OMe$, -W', $-CH_2W'$, -OW', $-OCH_2W'$, $-OCH_2CH_2W'$, $-OCH_2CH_2CH_2W'$,

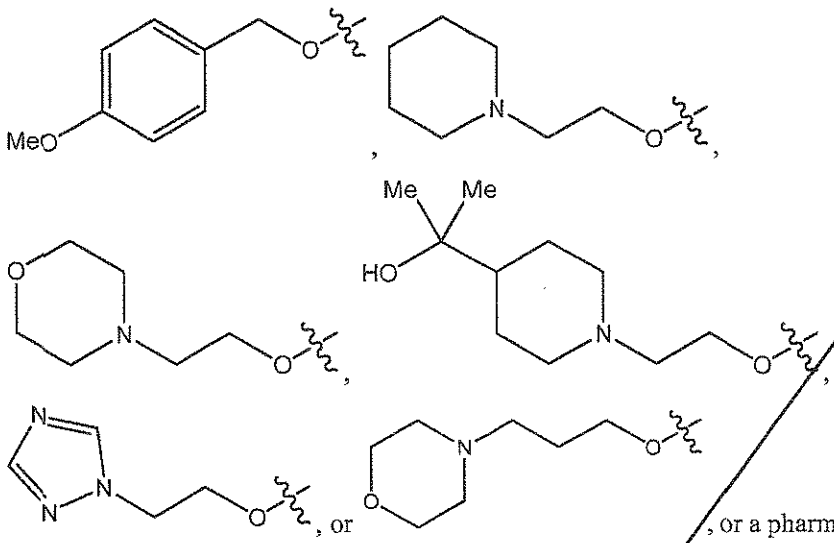
-NHW', -$NHCH_2W$', -$NHCH_2CH_2W$', -$NHCH_2CH_2CH_2W$', or -W'-C(=O)-W"; wherein W', if present, is selected from a 3-10 membered heterocyclyl comprising 1 or 2 heteroatoms selected from N, O, and S; a C_6-C_{10} aryl; or a 5-10 membered heteroaryl comprising 1, 2, 3, or 4 heteroatoms independently selected from N, O, or S; wherein the 3-10 membered heterocyclyl W' group may be monocyclic or bicyclic, and further wherein the 3-10 membered heterocyclyl, the C_6-C_{10} aryl, or the 5-10 membered heteroaryl W' groups are unsubstituted or are substituted with 1, 2, 3, or 4 substituents independently selected from –F, -Cl, -Br, -(C_1-C_6)alkyl, -$CH(CF_3)(OH)$, -(C_1-C_4)alkylene-NH_2, -(C_1-C_4)alkylene-NH-(C_1-C_4)alkylene-CF_3, -C(=O)NH_2, -SO_2-(C_1-C_6)alkyl, -CF_3, -CO_2H, -(C_1-C_4)alkylene-C(=O)-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-C(=O)-O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-C(=O)-OH, -(C_1-C_4)alkylene-OH, -OH, -O-(C_1-C_6)alkyl, or -SO_3H; and further wherein W' may include 0, 1, or 2 =O groups when W' is a 3-10 membered heterocyclyl, and further wherein the =O groups may be bonded to a ring carbon atom or a ring S atom; and further wherein W", if present, is a 3-10 membered heterocyclyl comprising 1, 2, or 3 heteroatoms selected from N, O, and S, wherein the 3-10 membered heterocyclyl W" group may be monocyclic or bicyclic, and further wherein the 3-10 membered heterocyclyl W" group is unsubstituted or is optionally substituted with 1, 2, 3, or 4 substituents independently selected from –F, -Cl, -Br, -I, -C≡N, -NO_2, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -OH, -NH_2, -NH((C_1-C_4)alkyl), -N((C_1-C_4)alkyl)$_2$, -CF_3, -CO_2H, -C(=O)-O-(C_1-C_4)alkyl, -SH, -S-(C_1-C_6)alkyl, -OCF_3, or -$OCHF_2$, or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, a stereoisomer of any of the foregoing, or a mixture thereof.

22. The compound of any one of Claims 1-20, wherein W is selected from -H, -F, -Cl, -OH, -OMe, -SO_2Me, -CH_2OH, -CH_2OMe, -OCH_2CH_2OH, -OCH_2CH_2OMe, or a group selected from





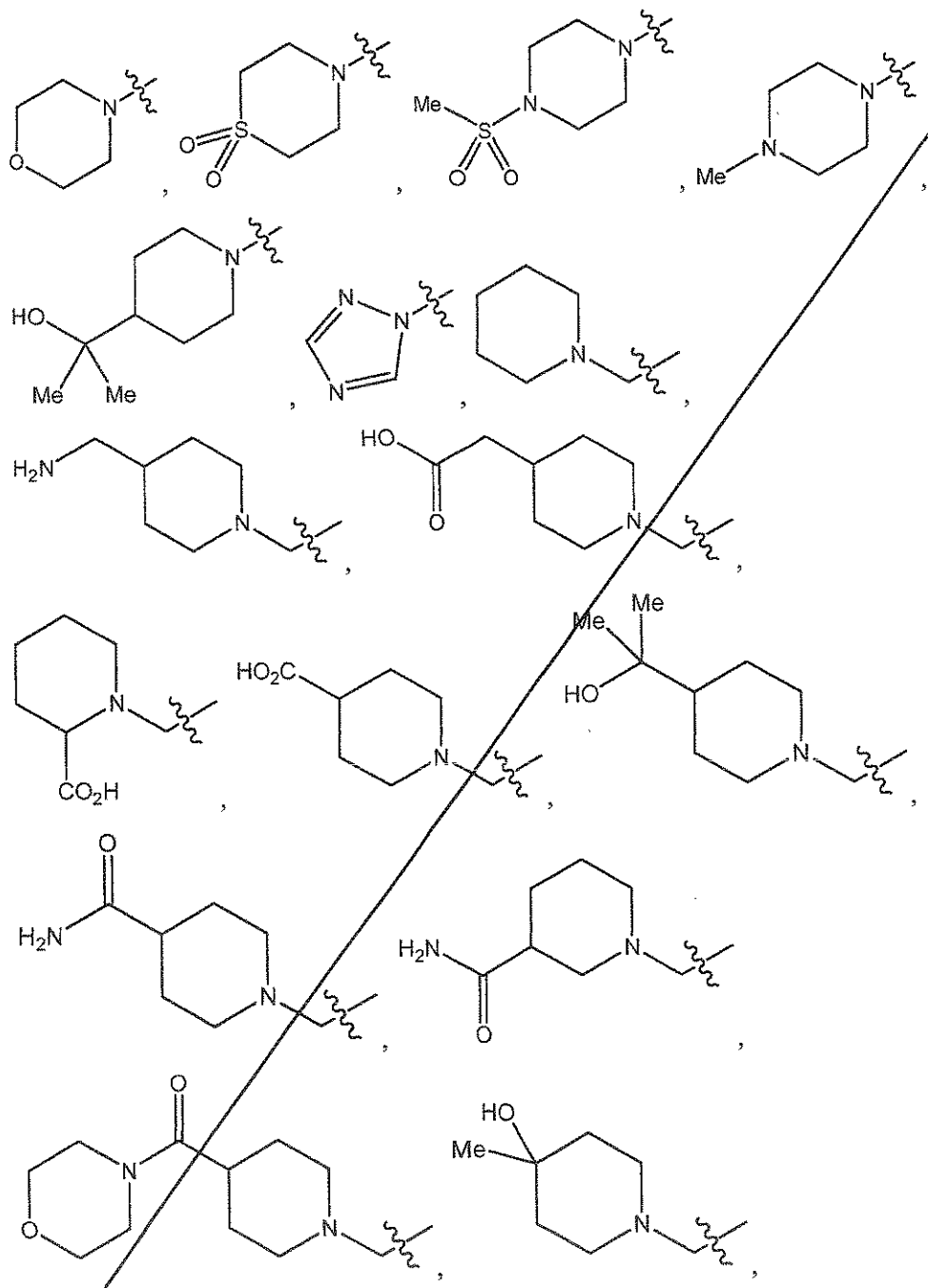


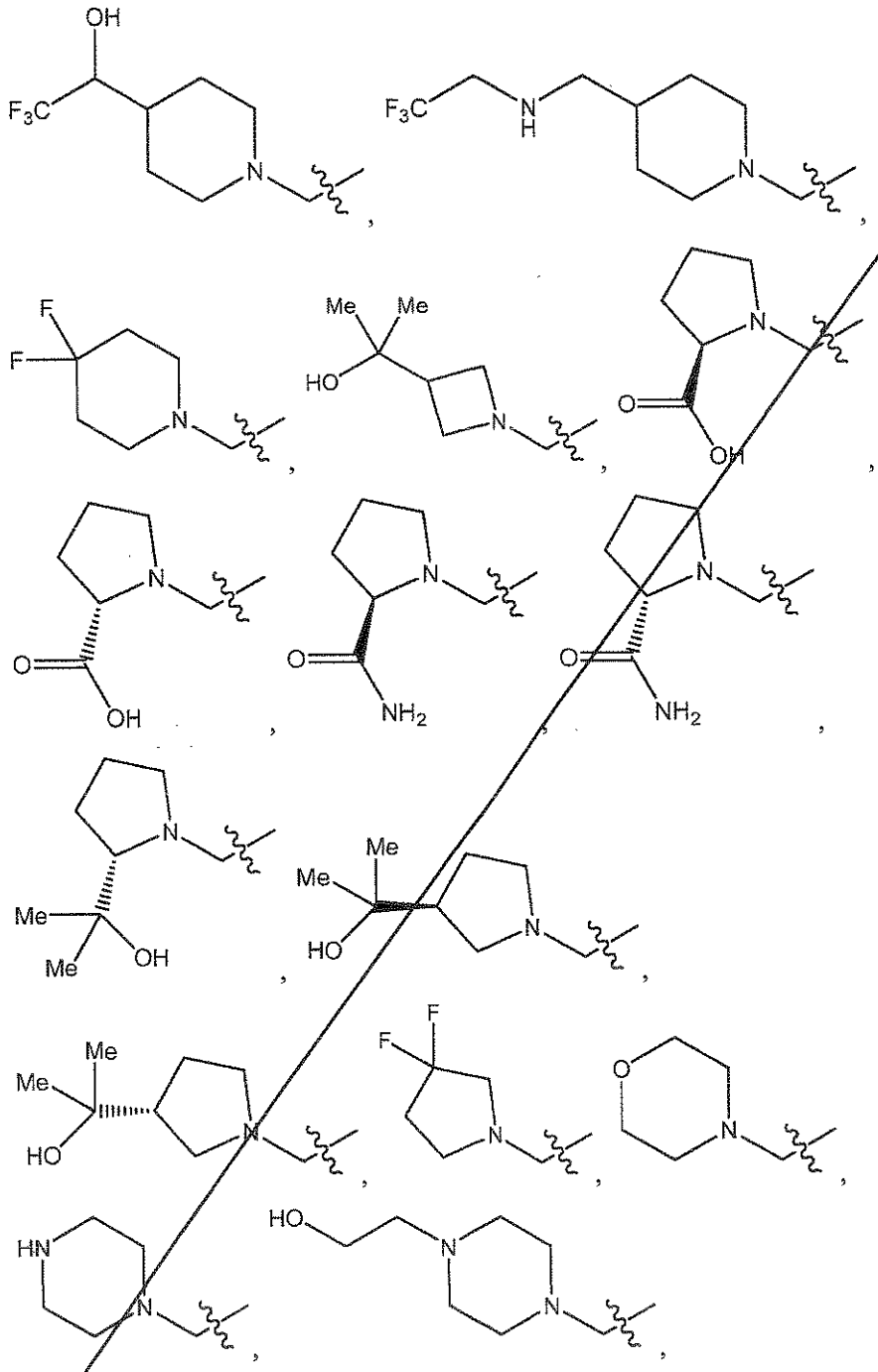


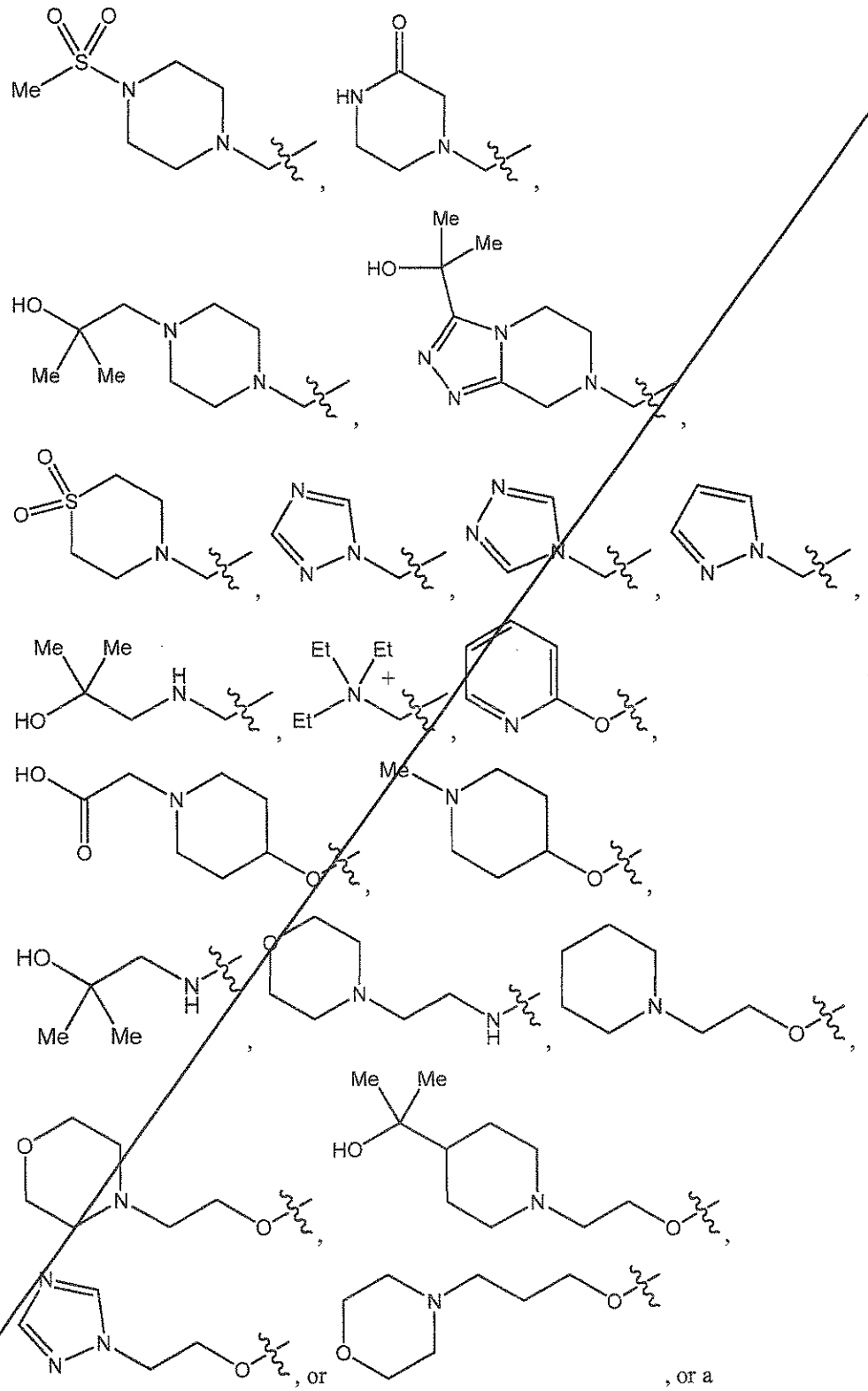
, or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, a stereoisomer of any of the foregoing, or a mixture thereof, wherein the symbol ~~~, when drawn across a bond, indicates the point of attachment to the rest of the molecule.

23. The compound of Claim 22, wherein W is not –H, -F, -Cl, –OH, or -OMe, or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, a stereoisomer of any of the foregoing, or a mixture thereof.

24. The compound of any one of Claims 1-20, wherein W is selected from -OH, $-SO_2Me$, $-CH_2OH$, $-CH_2OMe$, $-OCH_2CH_2OH$, $-OCH_2CH_2OMe$, or a group selected from



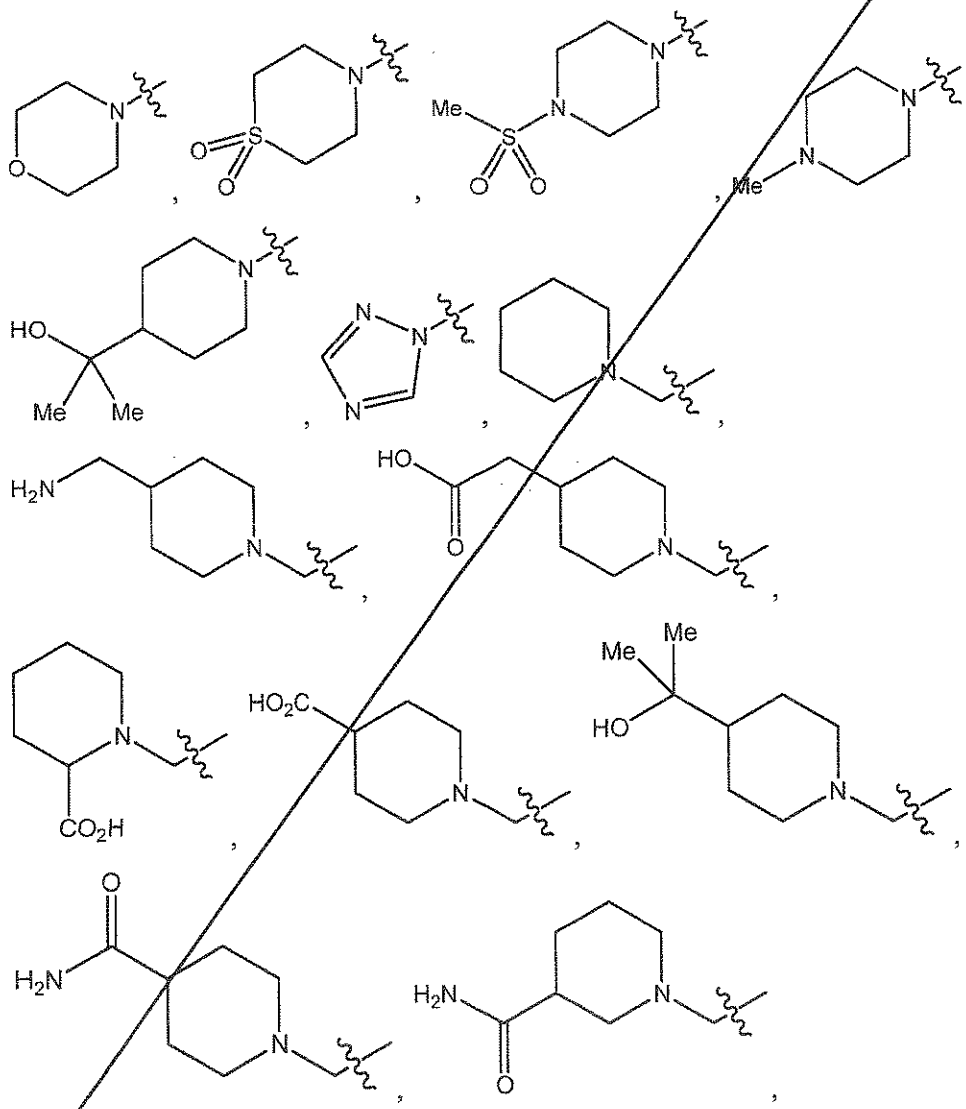


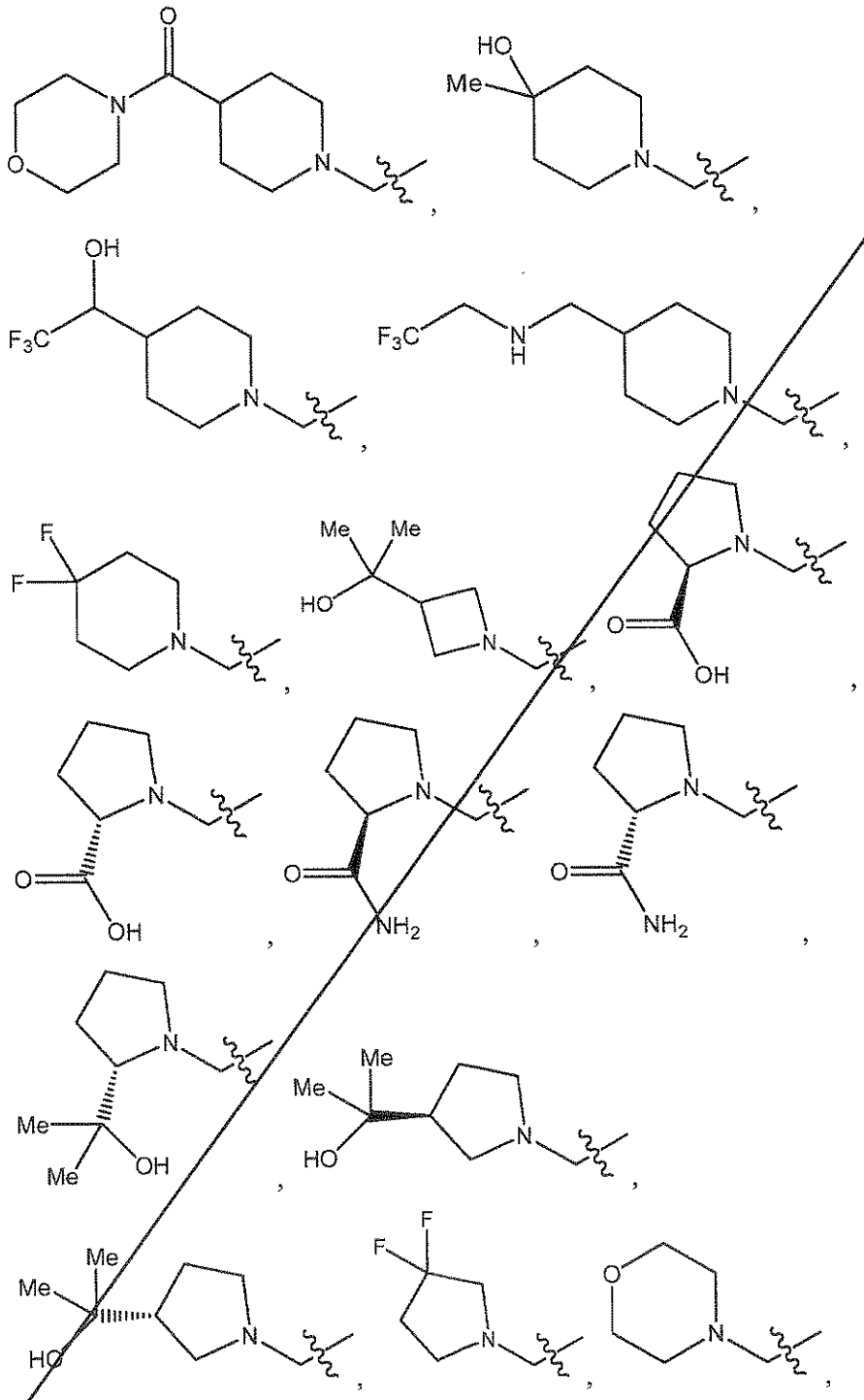


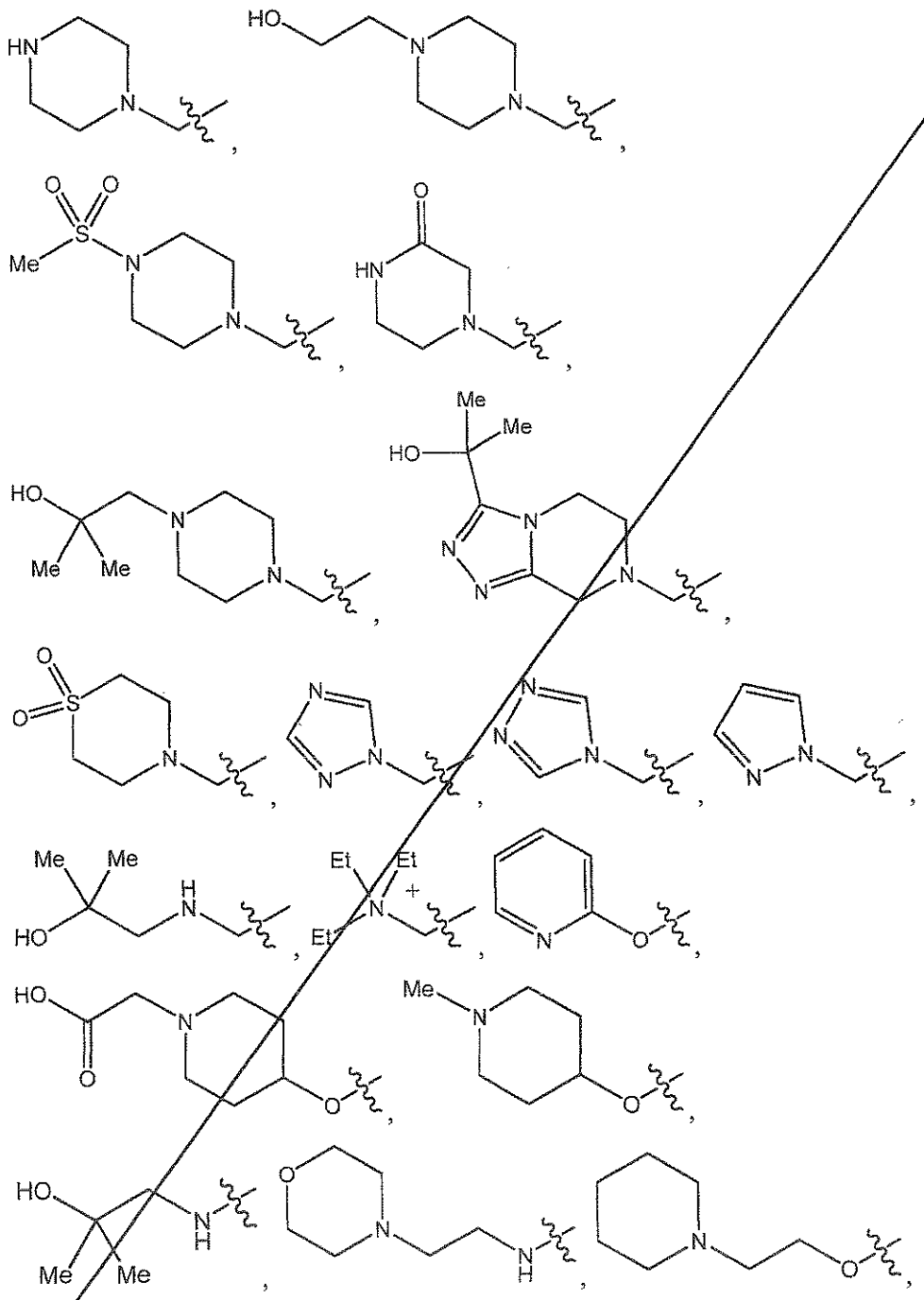
, or a

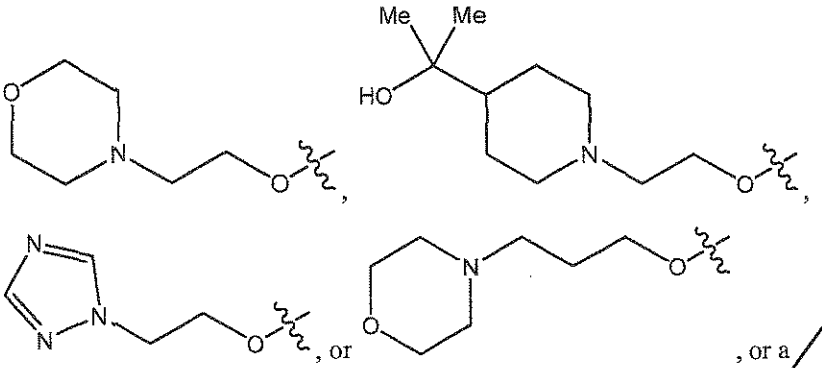
pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, a stereoisomer of any of the foregoing, or a mixture thereof, wherein the symbol ~~~, when drawn across a bond, indicates the point of attachment to the rest of the molecule.

25. The compound of any one of Claims 1-20, wherein W is selected from



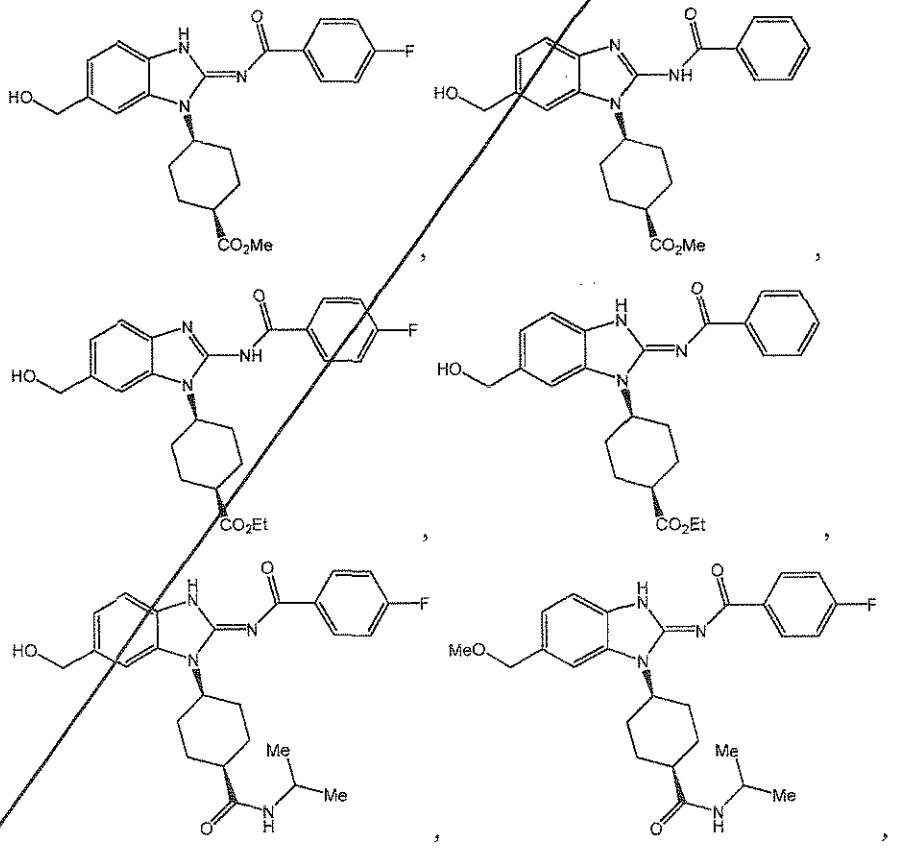


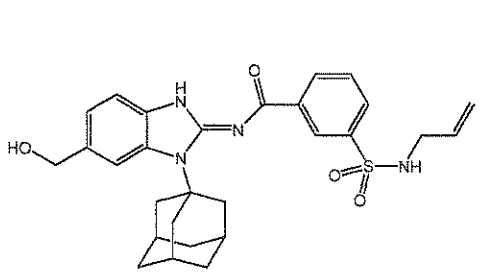




, or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, a stereoisomer of any of the foregoing, or a mixture thereof, wherein the symbol ~~~, when drawn across a bond, indicates the point of attachment to the rest of the molecule.

26. The compound of Claim 1, wherein the compound is selected from,

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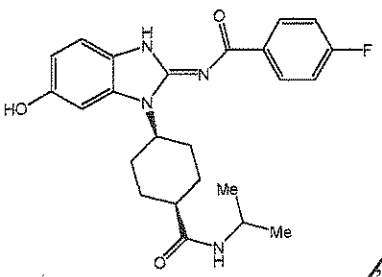
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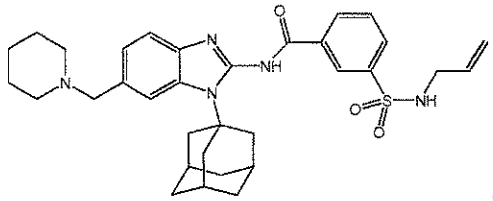
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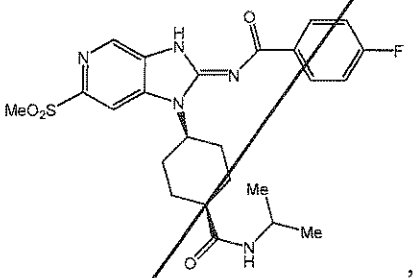
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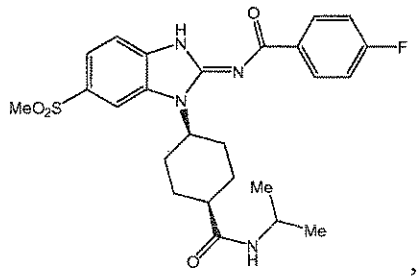
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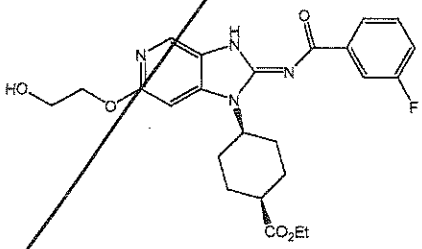
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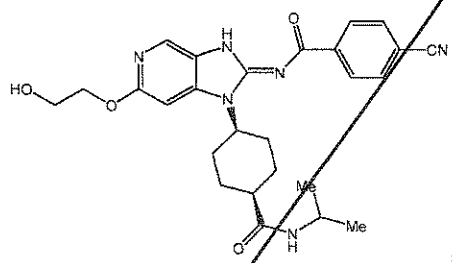
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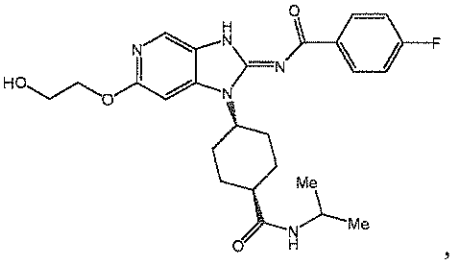
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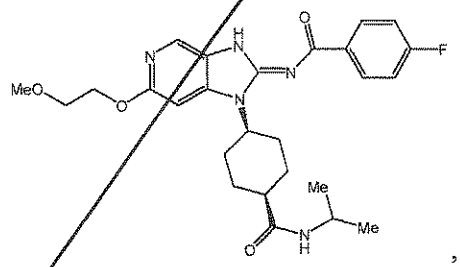
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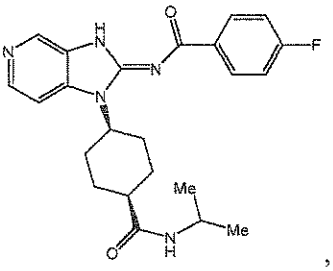

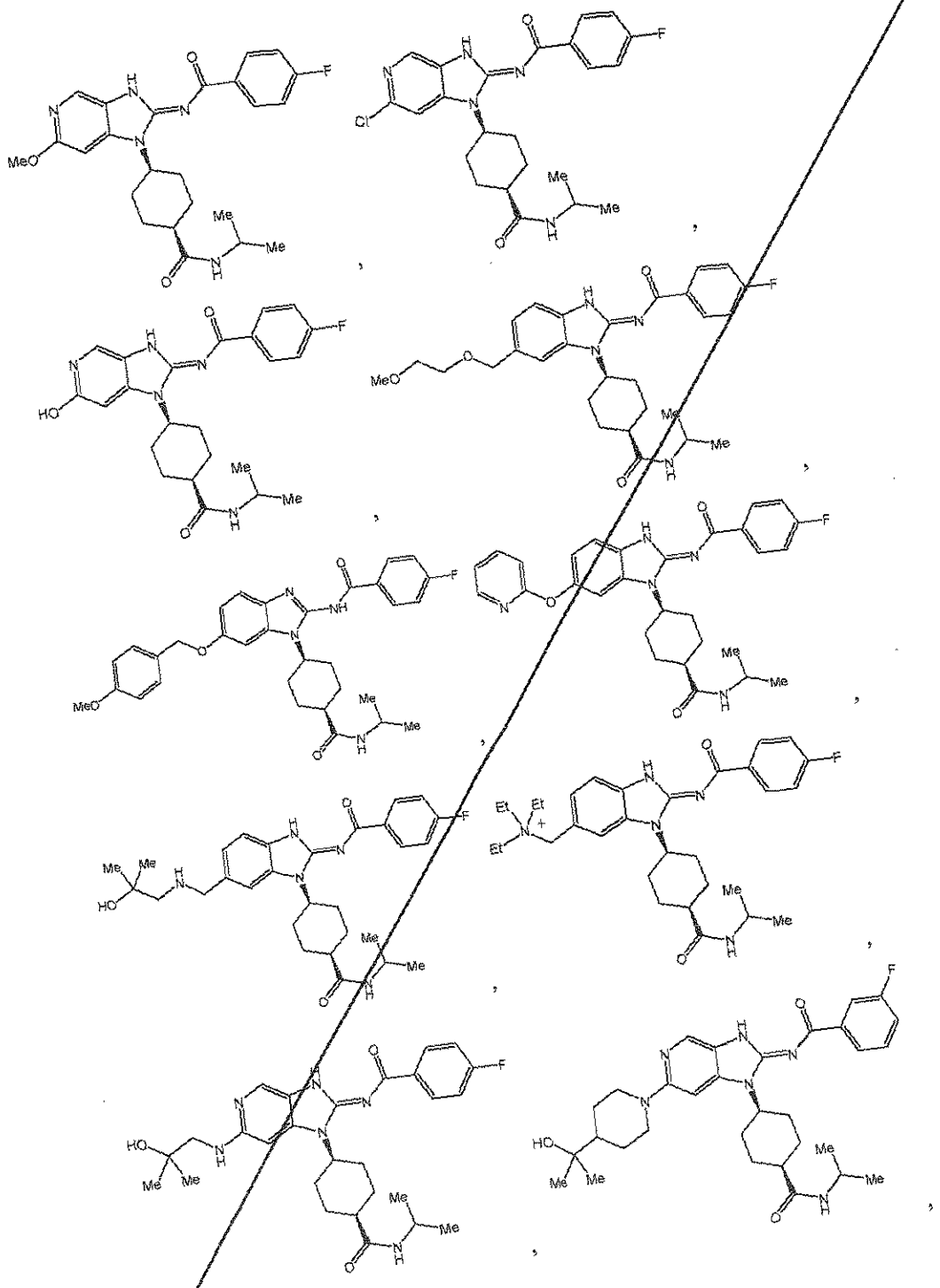

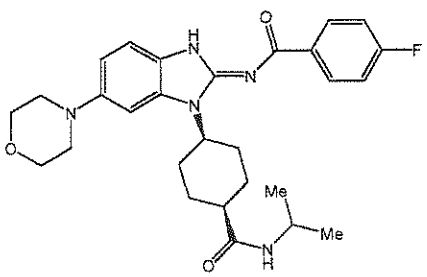
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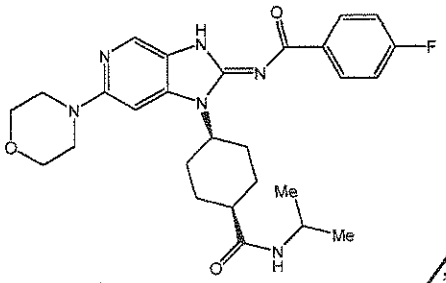
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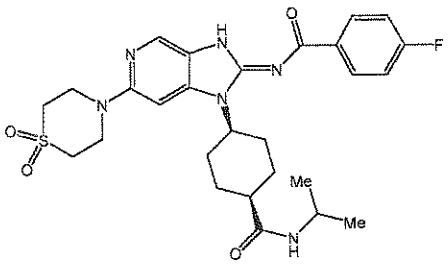
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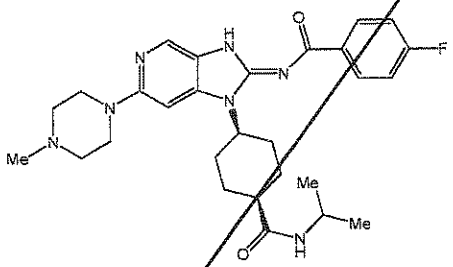
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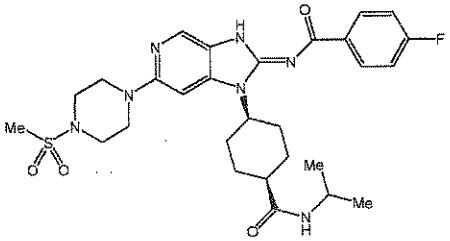
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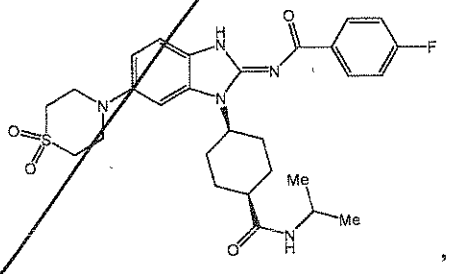
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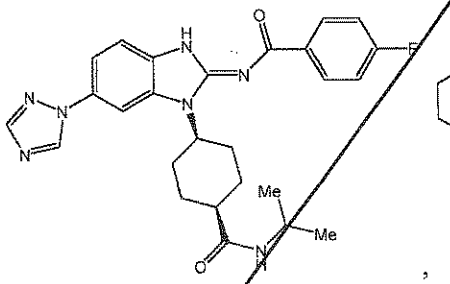
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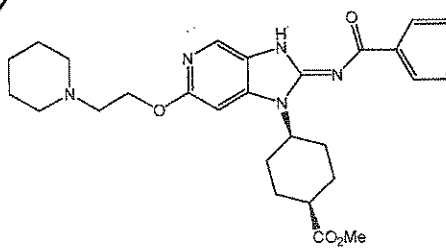
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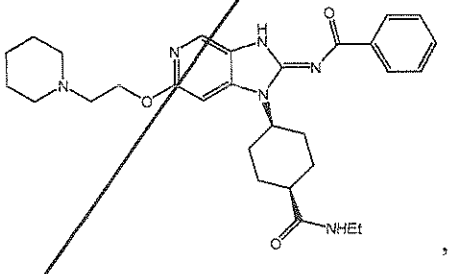
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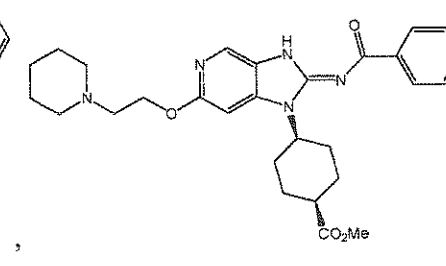
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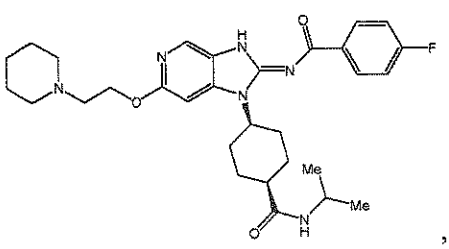
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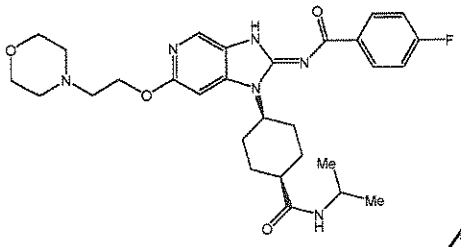
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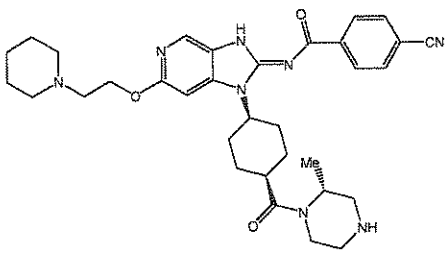
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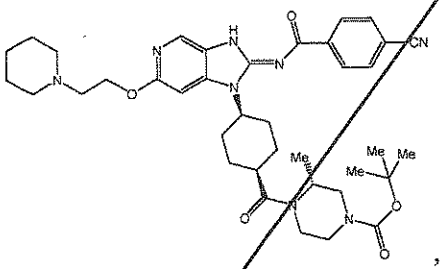
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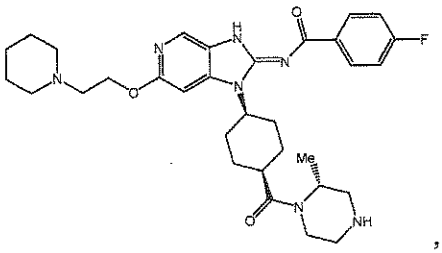
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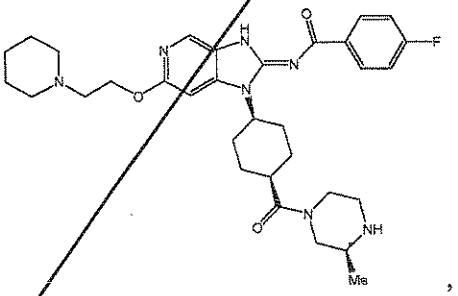
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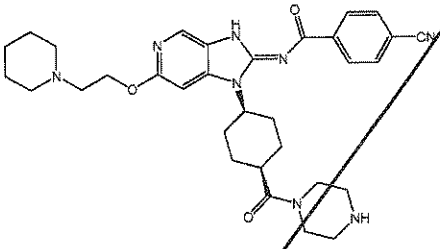
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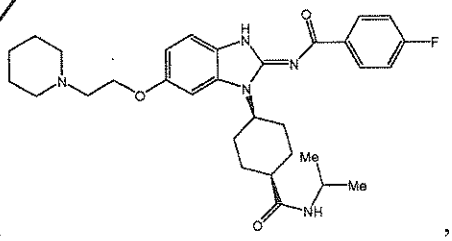
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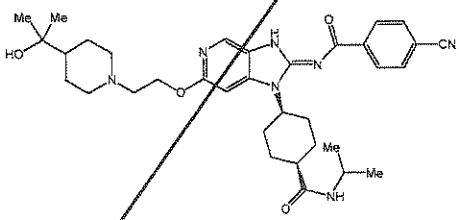
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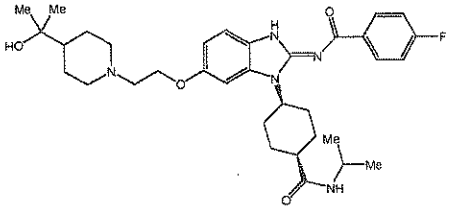
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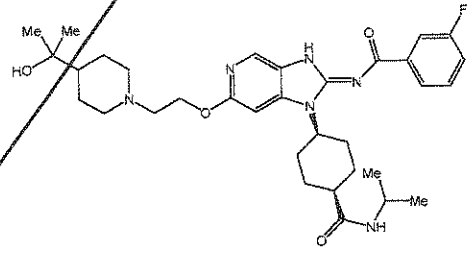
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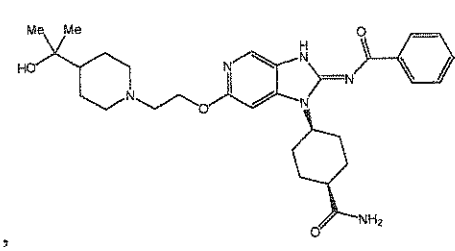
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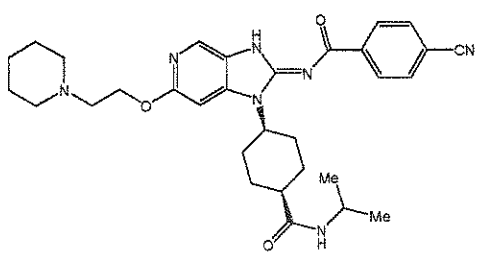
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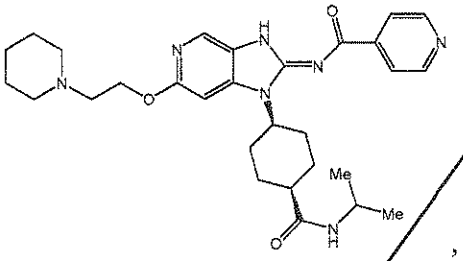
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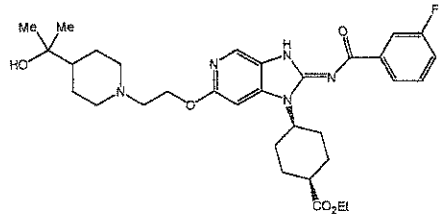
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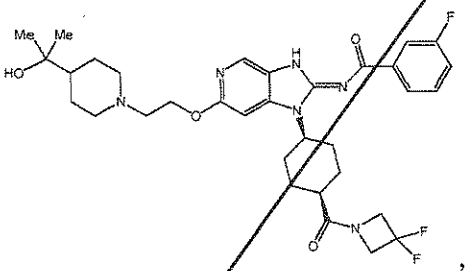
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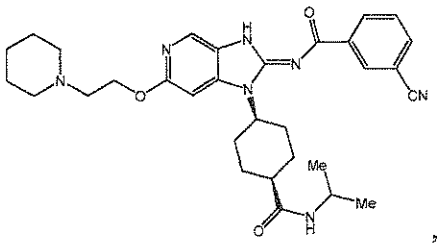
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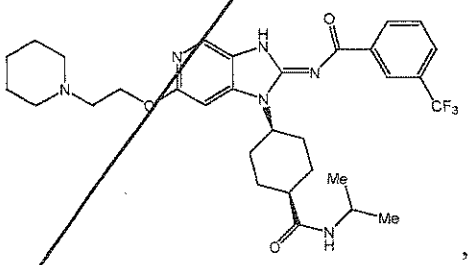
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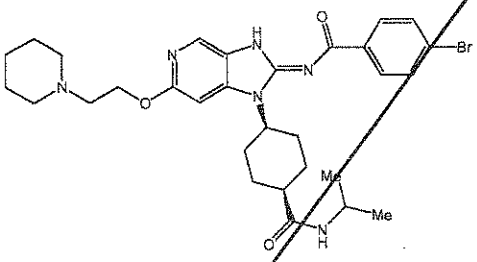
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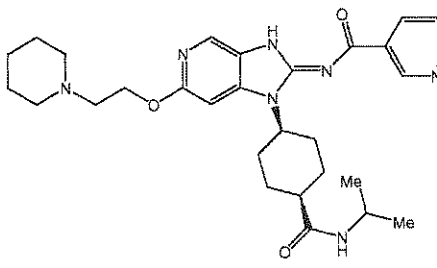
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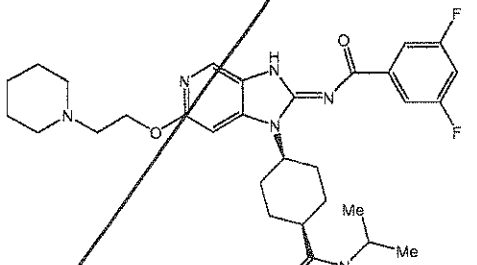
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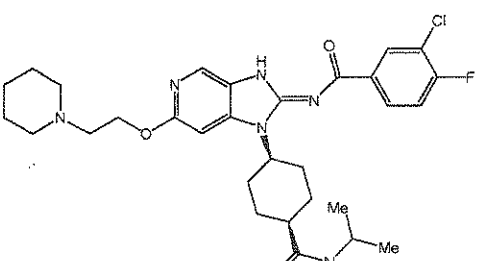
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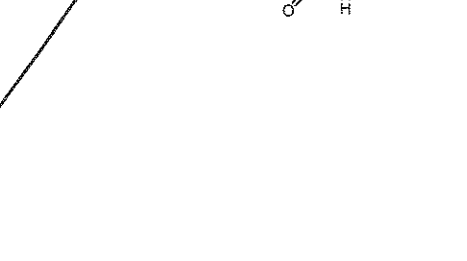
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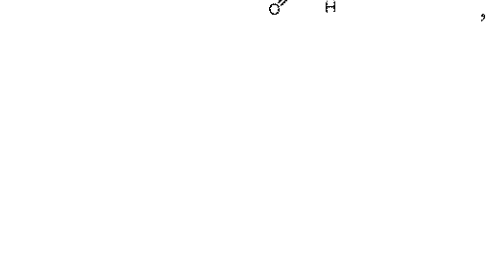
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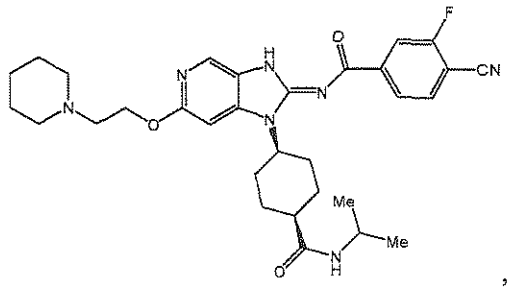

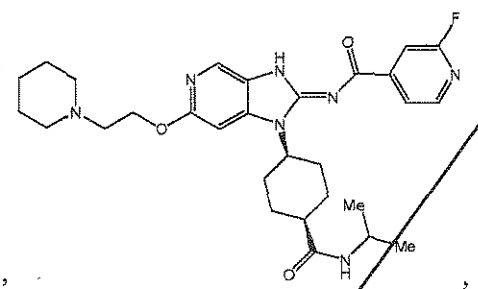

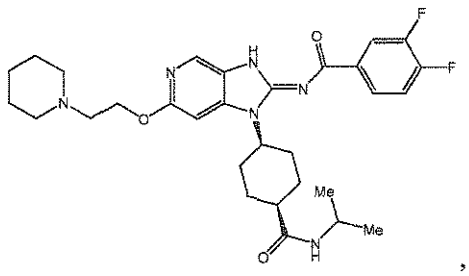

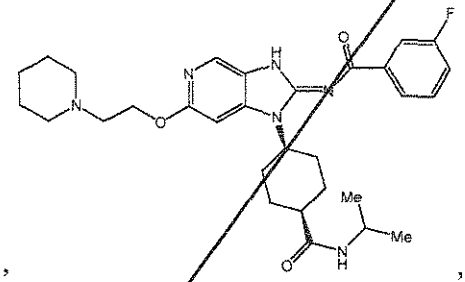

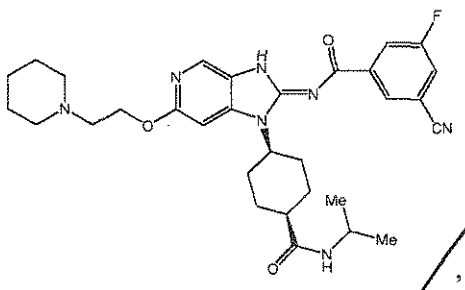

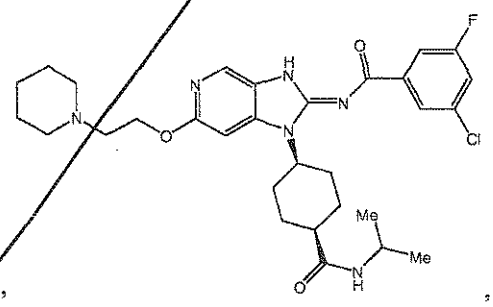

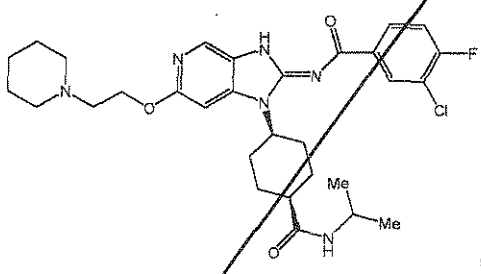

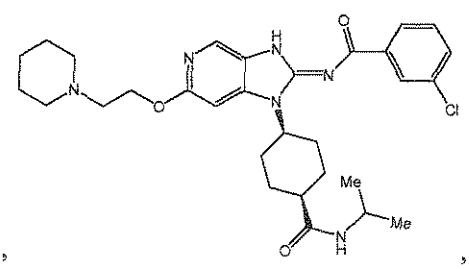

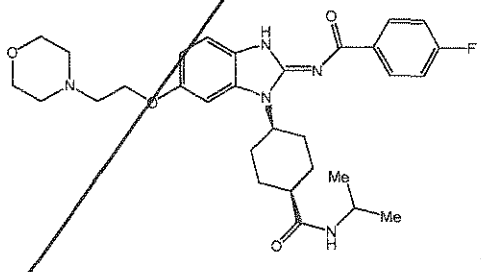

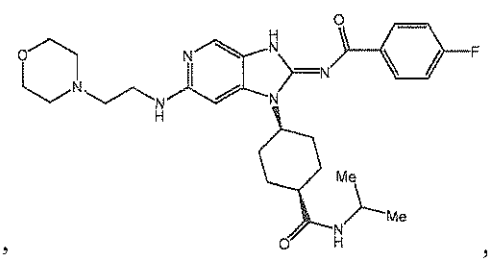

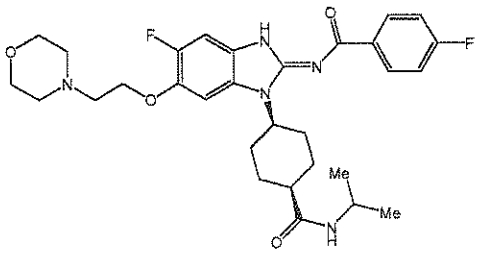
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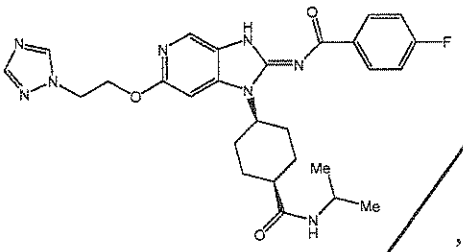
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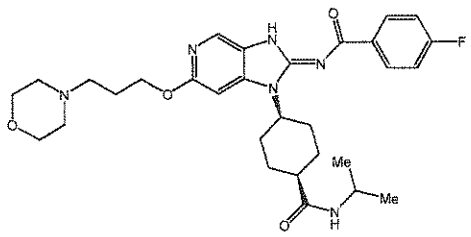
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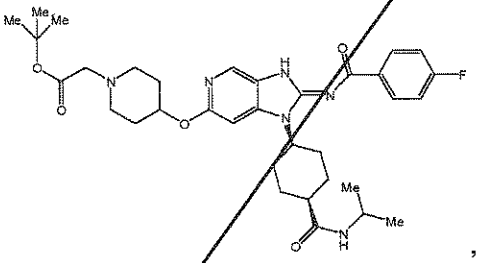
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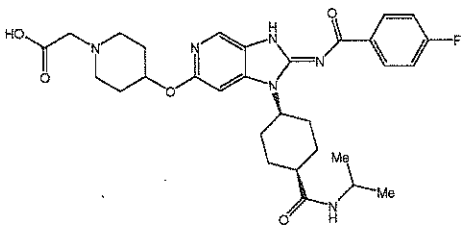
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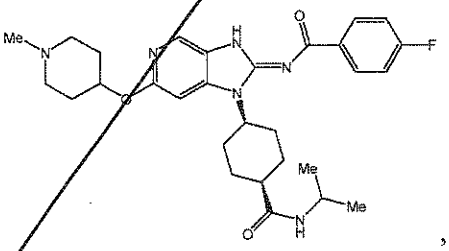
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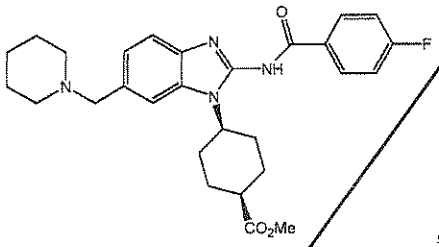
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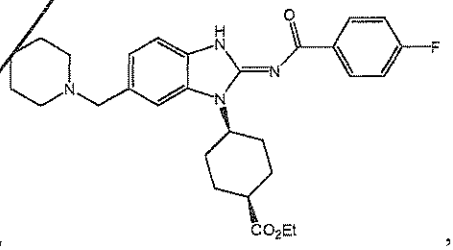
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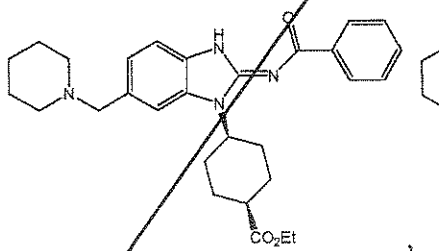
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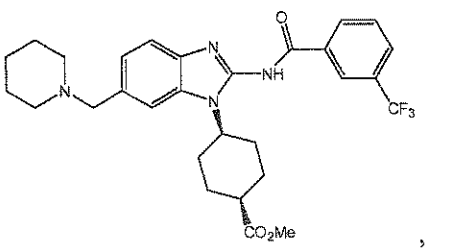
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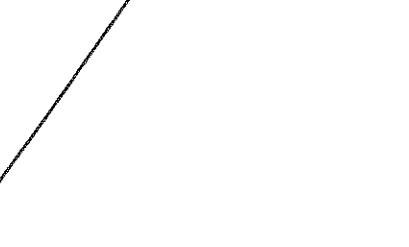
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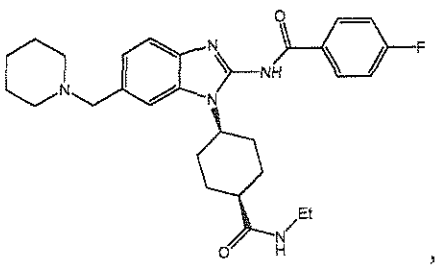
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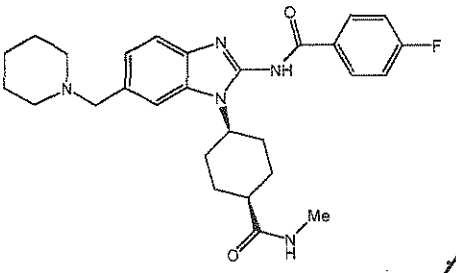
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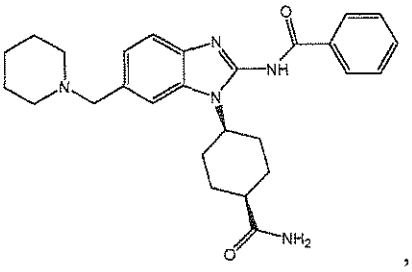
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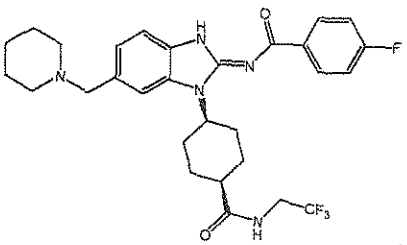

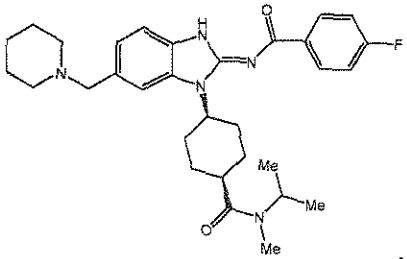

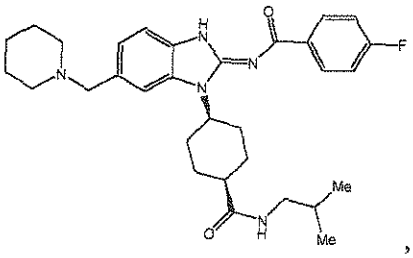

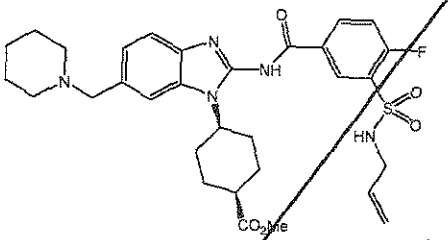

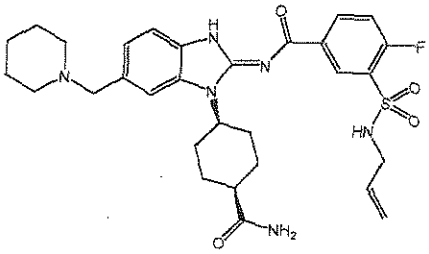

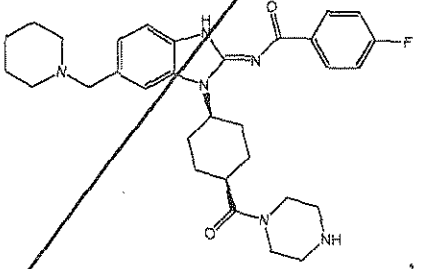

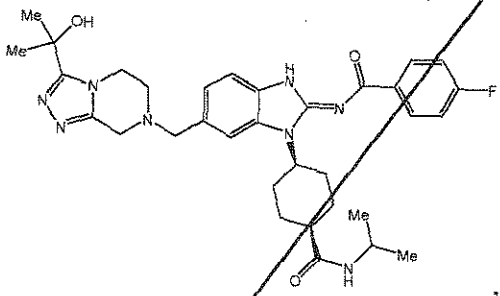

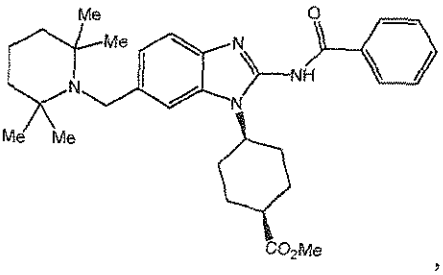

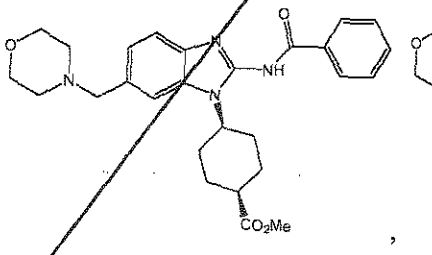

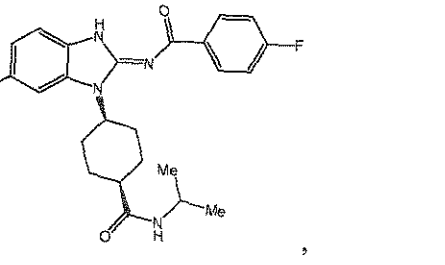



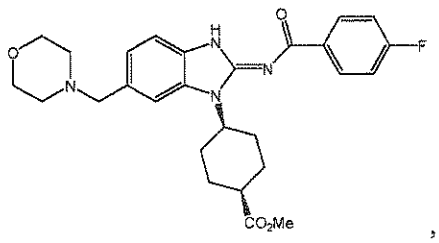
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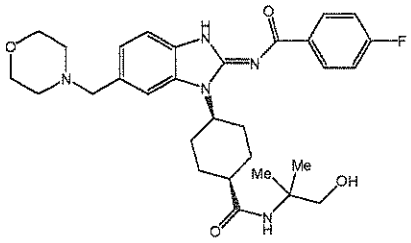
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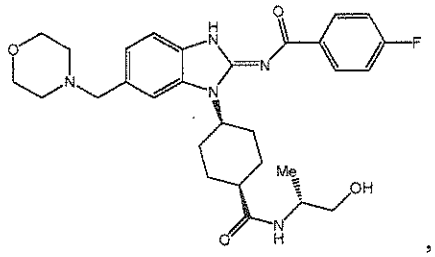
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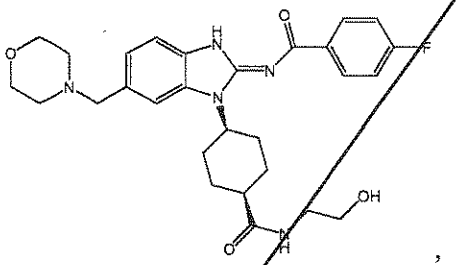
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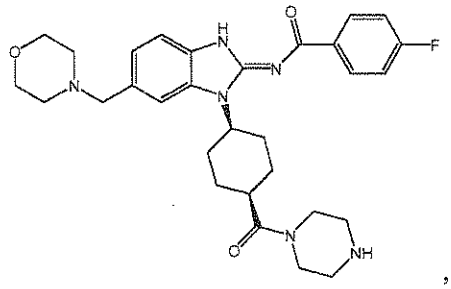
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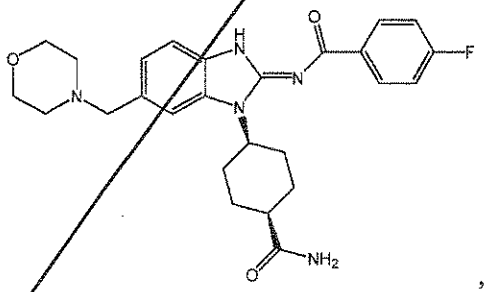
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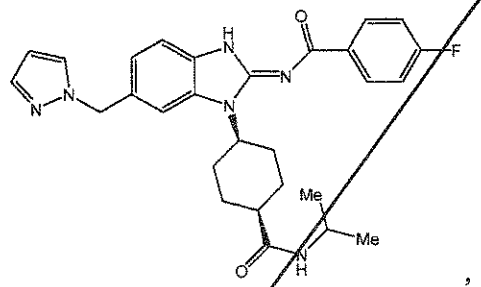
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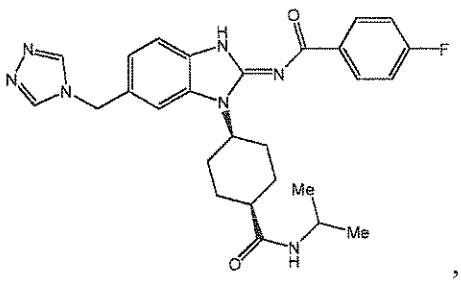
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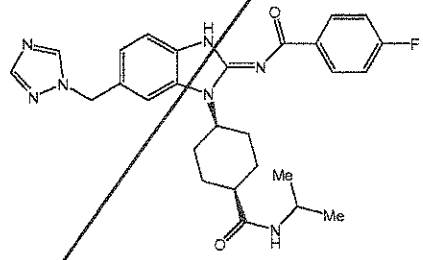
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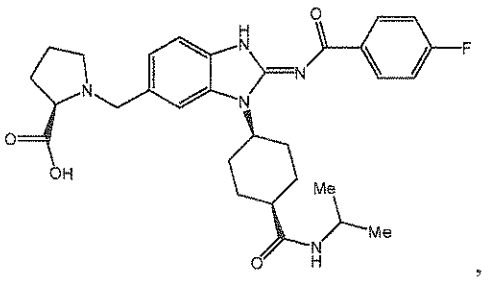
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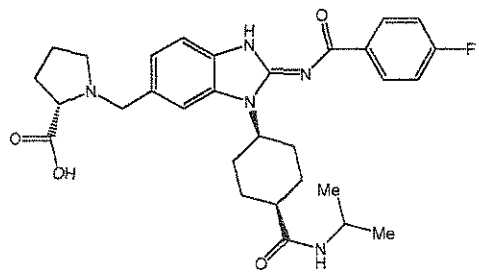
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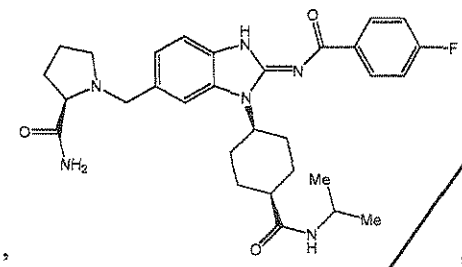
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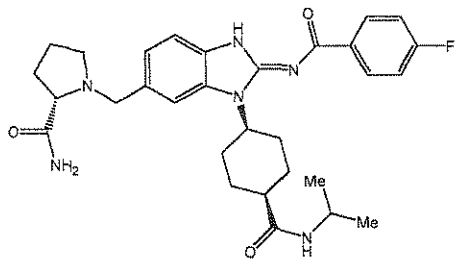
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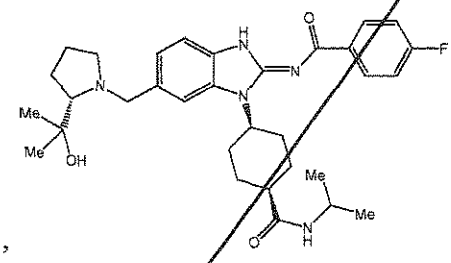
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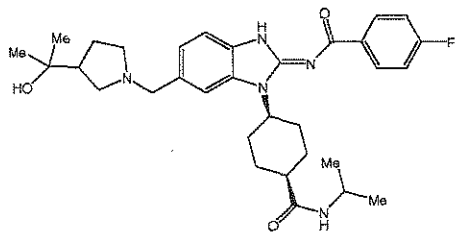
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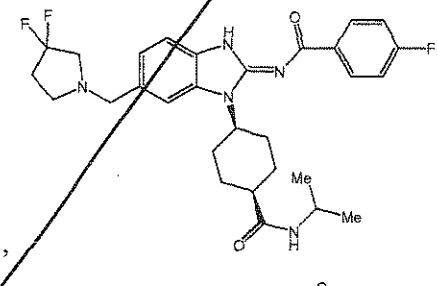
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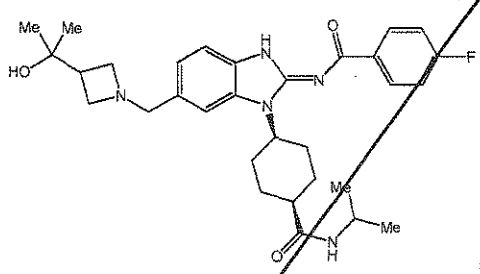
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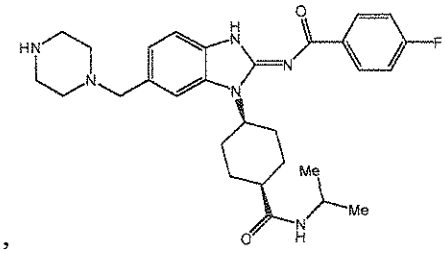
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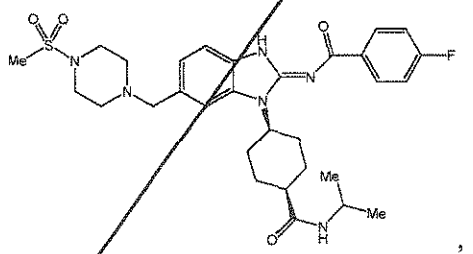
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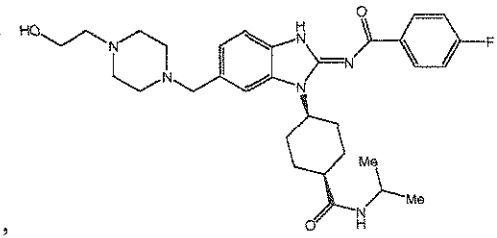
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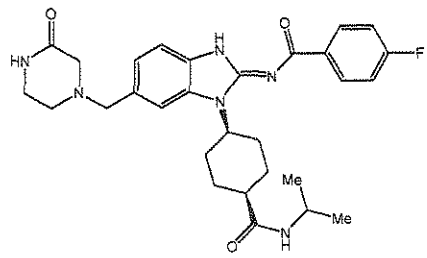
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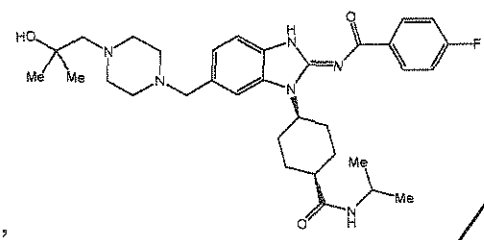
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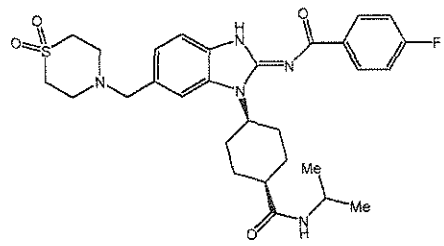
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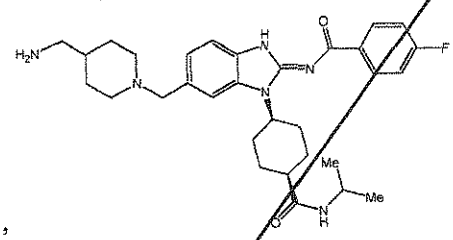
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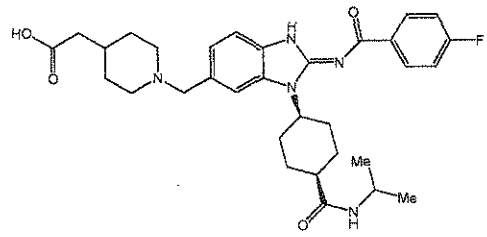
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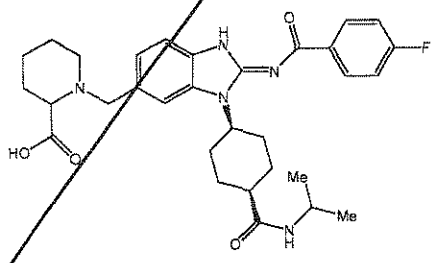
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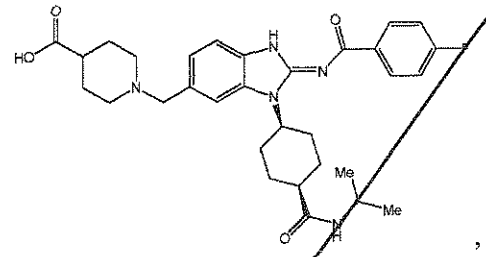
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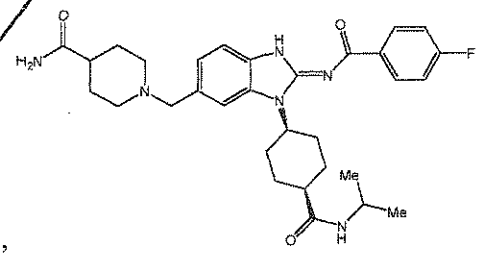
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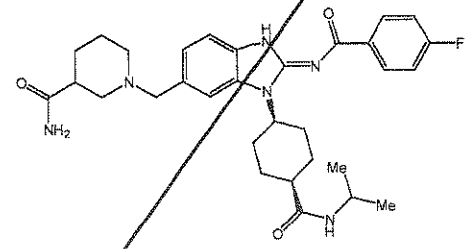
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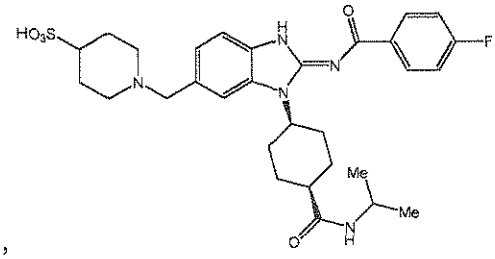
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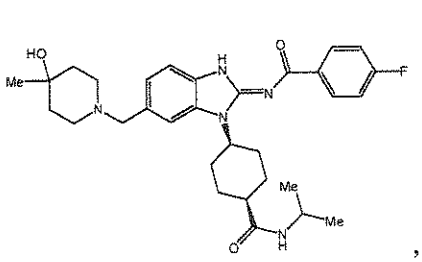
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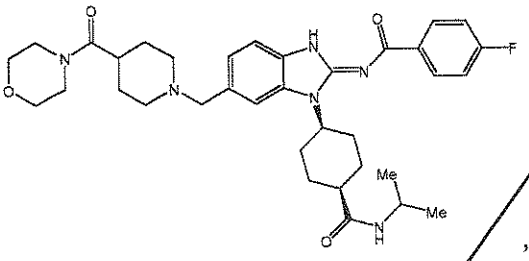
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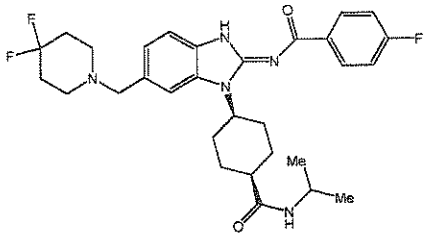
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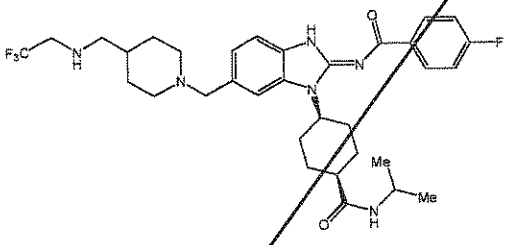
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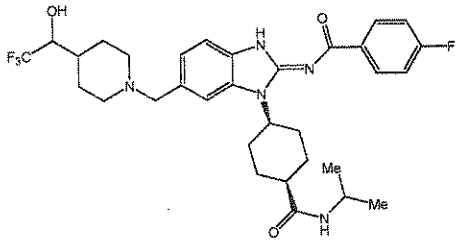
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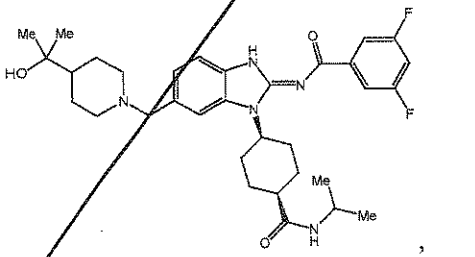
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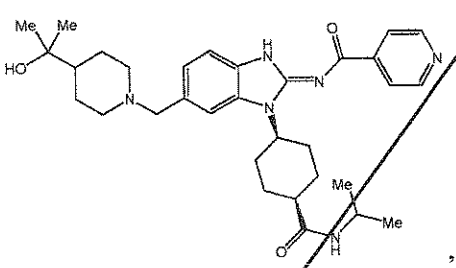
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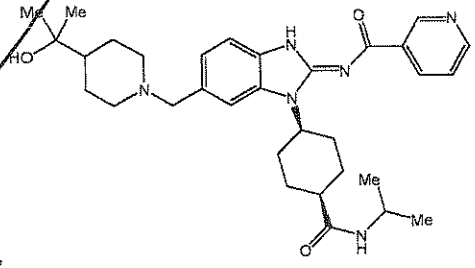
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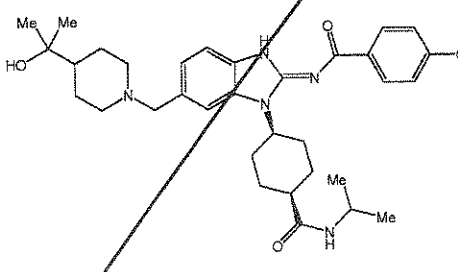
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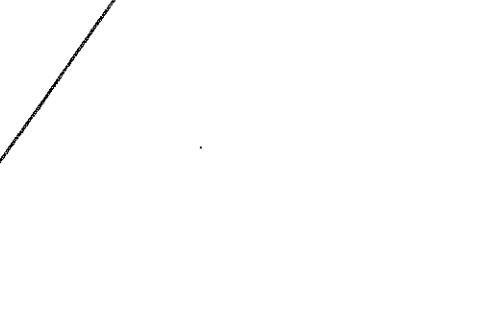
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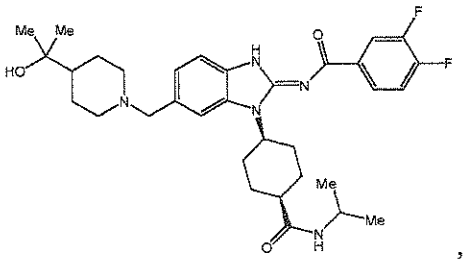
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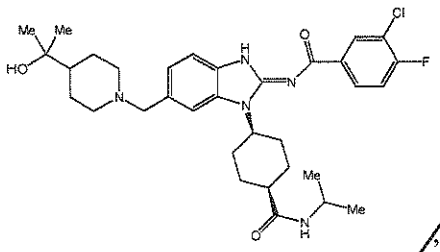
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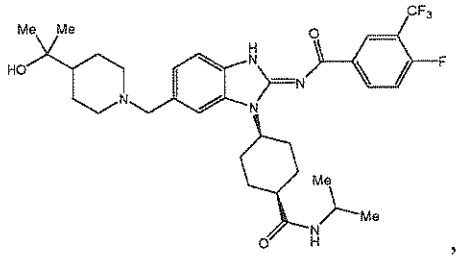
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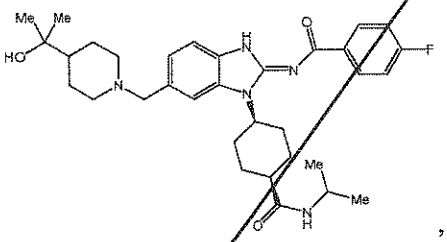
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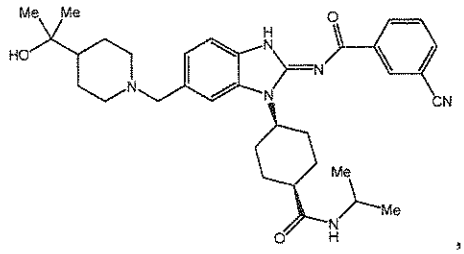
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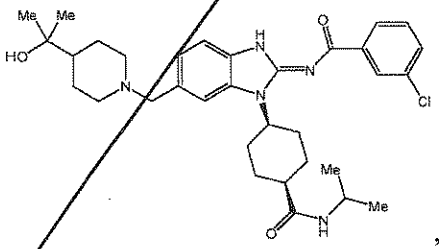
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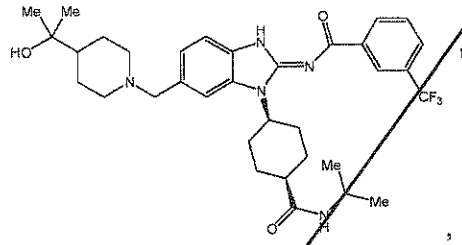
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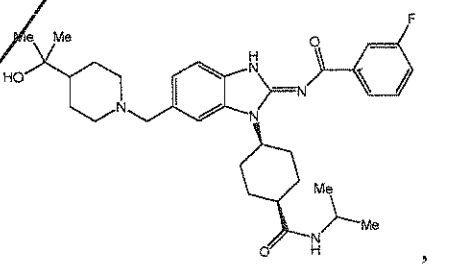
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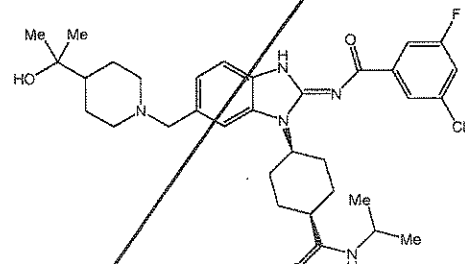
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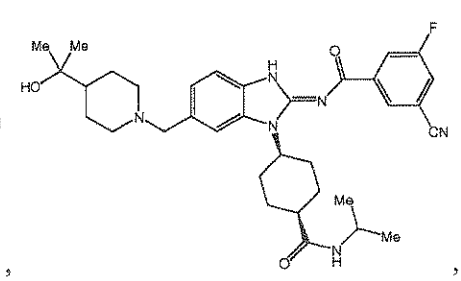
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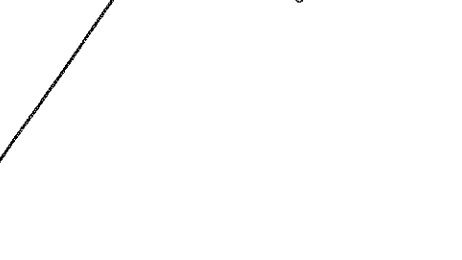
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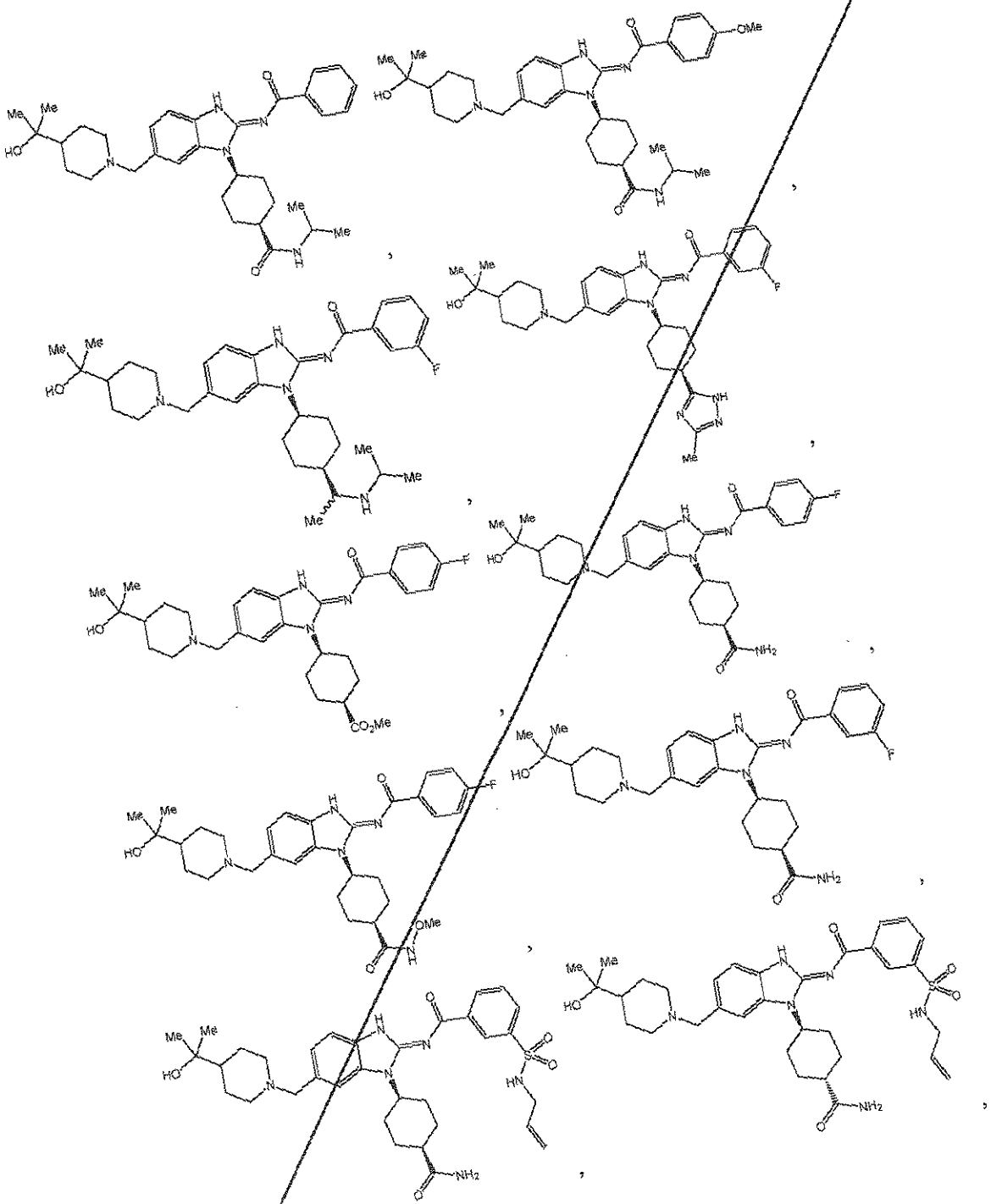

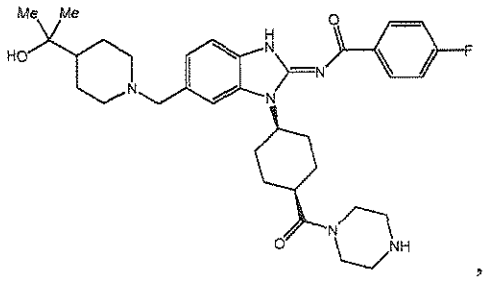
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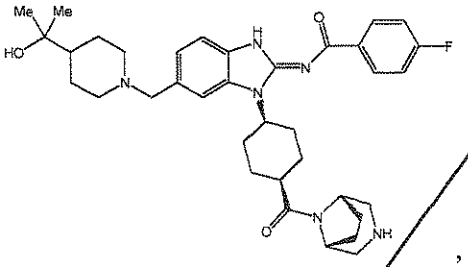
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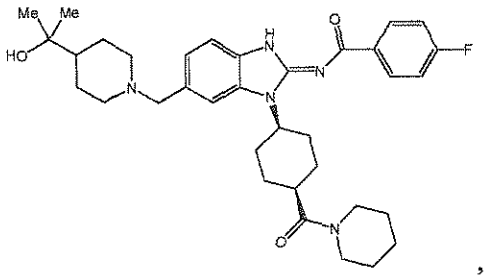
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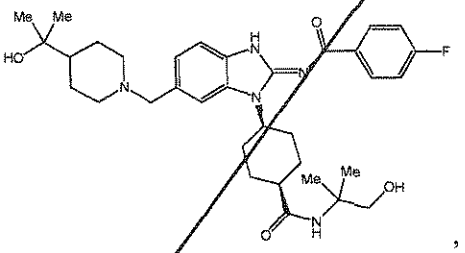
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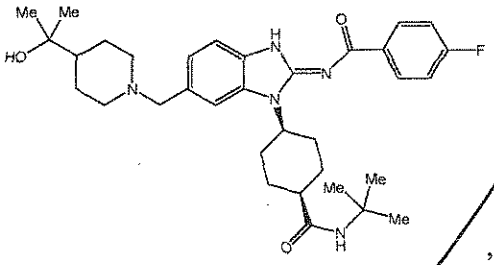

or , or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, a stereoisomer of any of the foregoing, or a mixture thereof.

27. A pharmaceutical composition, comprising a therapeutically effective amount of the compound or the pharmaceutically acceptable salt thereof, tautomer thereof, the pharmaceutically acceptable salt of the tautomer, the stereoisomer of any of the foregoing, or the mixture thereof according to any one of Claims 1-26 and at least one pharmaceutically acceptable excipient, carrier, or diluent.

28. A method of treating cancer, the method comprising: administering to a subject an effective amount of the compound or the pharmaceutically acceptable salt thereof, tautomer thereof, the pharmaceutically acceptable salt of the tautomer, the stereoisomer of any of the foregoing, or the mixture thereof according toany one of Claims 1-26 or the pharmaceutical composition of Claim 27.

29. The method of Claim 28, wherein the subject has a cancer that expresses an ALK fusion protein.

30. The method of Claim 29, wherein the ALK fusion protein is EML4-ALK fusion protein or NPM-ALK fusion protein.

31. The method of Claim 30, wherein the subject is a human cancer patient, and the cancer is selected from adenocarcinoma, lung cancer, non-small cell lung carcinoma, breast cancer, colorectal cancer, lymphoma, neuroblastoma, ovarian cancer, mesothelioma, melanoma, glioblastoma, diffuse large B-cell lymphomas, systemic histiocytosis, or inflammatory myofibroblastic tumors.

32. A method of treating a condition where it is desired to inhibit ALK activity, comprising administering to a subject an effective amount of the compound or the pharmaceutically acceptable salt thereof, tautomer thereof, the pharmaceutically acceptable salt of the tautomer, the stereoisomer of any of the foregoing, or the mixture thereof according toany one of Claims 1-26 or the pharmaceutical composition of Claim 27.

33. The compound or the pharmaceutically acceptable salt thereof, tautomer thereof, the pharmaceutically acceptable salt of the tautomer, the stereoisomer of any of the foregoing, or the mixture thereof according to any one of Claims 1-26 or the pharmaceutical composition of Claim 27 for use in treating cancer.

34. The compound or the pharmaceutically acceptable salt thereof, tautomer thereof, the pharmaceutically acceptable salt of the tautomer, the stereoisomer of any of the foregoing, or the mixture thereof according toany one of Claims 1-26 or the pharmaceutical composition of Claim 27 for use in inhibiting ALK.

35. The compound or the pharmaceutically acceptable salt thereof, tautomer thereof, the pharmaceutically acceptable salt of the tautomer, the stereoisomer of any of the foregoing, or the mixture thereof according to any one of Claims 1-26 or the pharmaceutical composition of Claim 27 for use in treating cancer, wherein the cancer expresses an ALK fusion protein.

36. The compound or the pharmaceutically acceptable salt thereof, tautomer thereof, the pharmaceutically acceptable salt of the tautomer, the stereoisomer of any of the foregoing, or the mixture thereof according to any one of Claims 1-26 or the pharmaceutical composition of Claim 28 for use in treating cancer, wherein the cancer expresses EML4-ALK fusion protein or NPM-ALK fusion protein.

37. The use of the compound or the pharmaceutically acceptable salt thereof, tautomer thereof, the pharmaceutically acceptable salt of the tautomer, the stereoisomer of any of the foregoing, or the mixture thereof according to any one of Claims 1-26 in the preparation of a medicament for treating cancer.

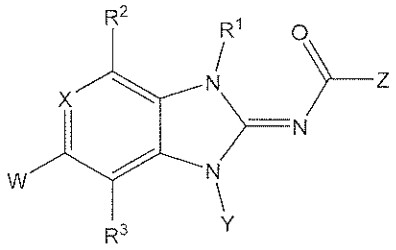
38. The use of the compound or the pharmaceutically acceptable salt thereof, tautomer thereof, the pharmaceutically acceptable salt of the tautomer, the stereoisomer of any of the foregoing, or the mixture thereof according to any one of Claims 1-26 in the preparation of a medicament for inhibiting ALK.

39. The use of the compound or the pharmaceutically acceptable salt thereof, tautomer thereof, the pharmaceutically acceptable salt of the tautomer, the stereoisomer of any of the foregoing, or the mixture thereof according to any one of Claims 1-26 in the preparation of a medicament for treating cancer, wherein the cancer expresses an ALK fusion protein.

40. The use of the compound or the pharmaceutically acceptable salt thereof, tautomer thereof, the pharmaceutically acceptable salt of the tautomer, the stereoisomer of any of the foregoing, or the mixture thereof according to any one of Claims 1-26 in the preparation of a medicament for treating cancer, wherein the cancer expresses EML4-ALK fusion protein or NPM-ALK fusion protein.

CLAIMS

1. A compound of Formula I:



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or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, or a stereoisomer of any of the foregoing, wherein:

R^1 is -H;

R^2 is -H;

R^3 is –H;

X is selected from CR^4;

R^4 is –H;

Y is selected from a C_3-C_{12} cycloalkyl or a 3-10 membered heterocyclyl comprising 1, 2, or 3 heteroatoms selected from O, S, or N; wherein the C_3-C_{12} cycloalkyl and the 3-10 membered heterocyclyl may be monocyclic, bicyclic, or tricyclic, and further wherein the C_3-C_{12} cycloalkyl and the 3-10 membered heterocyclyl comprise a substituent selected from -C(=O)NH_2, -C(=O)NH((C_1-C_6)alkyl), -C(=O)NH-(C_1-C_4)alkylene-CF_3, -C(=O)NH-(C_1-C_4)alkylene-F, -C(=O)NH-(C_2-C_4)alkenyl, -C(=O)N((C_1-C_6)alkyl)$_2$, -C(=O)NH-OH ,-C(=O)NH-O-(C_1-C_6)alkyl, -C(=O)NH-Y", -C(=O)-(C_1-C_4)alkylene-CF_3, -C(=O)N-(C_1-C_4)alkylene-F, -C(=O)-(C_2-C_4)alkenyl, -C(=O)-(C_1-C_4)alkylene-NH_2, -C(=O)-(C_1-C_4)alkylene-NH((C_1-C_4)alkyl), -C(=O)-(C_1-C_4)alkylene-N((C_1-C_4)alkyl)$_2$, -C(=O)NH-(C_1-C_4)alkylene-OH, -C(=O)NH-(C_1-C_4)alkylene-O-(C_1-C_6)alkyl, -C(=O)NH-(C_1-C_4)alkylene-Y", -C(=O)-(C_1-C_6)alkyl, -C(=O)-Y", -CO_2H, -C(=O)-O-(C_1-C_6)alkyl, -C(=O)NH-(C_1-C_4)alkylene-NH_2, -C(=O)NH-(C_1-C_4)alkylene-NH((C_1-C_6)alkyl), and -C(=O)NH-(C_1-C_4)alkylene-N((C_1-C_6)alkyl)$_2$, -(C_1-C_4)alkylene-NH-C(=O)-(C_1-C_6)alkyl; and

wherein Y optionally further comprises 1 or 2 substituents selected from Y', -F, -Cl, -Br, -I, -C≡N, -NO_2, -OH, -O-(C_1-C_6)alkyl, -SH, -S-(C_1-C_6)alkyl, -OCF_3, -$OCHF_2$, -CF_3, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -NH_2, -NH((C_1-C_4)alkyl), -N((C_1-C_4)alkyl)$_2$, -$NHSO_2$-(C_1-C_6)alkyl, -NHC(=O)-(C_1-C_6)alkyl, -C(=O)NH_2, -C(=O)NH((C_1-C_6)alkyl), -C(=O)NH-(C_1-C_4)alkylene-CF_3, -C(=O)NH-(C_1-C_4)alkylene-F, -C(=O)NH-(C_2-C_4)alkenyl, -C(=O)N((C_1-C_6)alkyl)$_2$, -C(=O)NH-OH ,-C(=O)NH-O-(C_1-C_6)alkyl, -C(=O)NH-Y", -C(=O)-(C_1-C_4)alkylene-CF_3, -C(=O)N-(C_1-C_4)alkylene-F, -C(=O)-(C_2-C_4)alkenyl, -C(=O)-(C_1-C_4)alkylene-NH_2, -C(=O)-(C_1-C_4)alkylene-NH((C_1-C_4)alkyl), -C(=O)-(C_1-C_4)alkylene-N((C_1-C_4)alkyl)$_2$, -C(=O)NH-(C_1-C_4)alkylene-OH, -C(=O)NH-(C_1-C_4)alkylene-O-(C_1-C_6)alkyl, -C(=O)NH-(C_1-C_4)alkylene-Y", -C(=O)-(C_1-C_6)alkyl, -C(=O)-Y", -CO_2H, -C(=O)-O-(C_1-C_6)alkyl, -C(=O)NH-(C_1-C_4)alkylene-NH_2, -C(=O)NH-(C_1-C_4)alkylene-NH((C_1-C_6)alkyl), and -C(=O)NH-(C_1-C_4)alkylene-N((C_1-C_6)alkyl)$_2$, -SO_2NH_2, -SO_2NH((C_1-C_6)alkyl), -SO_2N((C_1-C_6)alkyl)$_2$, -SO_2NH((C_2-C_4)alkenyl), -SO_2NH((C_2-C_4)alkynyl), -SO_2NH-Y", -SO_2NH-(C_1-C_4)alkylene-OH, -SO_2NH-(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2-Y", -SO-(C_1-C_6)alkyl, -(C_1-C_4)alkylene-NH-C(=O)-(C_1-C_6)alkyl, -(C_1-C_4)alkylene-NH-(C_1-C_6)alkyl, -(C_1-C_4)alkylene-N((C_1-C_6)alkyl)$_2$ -(C_1-C_4)alkylene-OH, -(C_1-C_4)alkylene-O-(C_1-C_6)alkyl, -(C_1-C_4)alkylene-C(=O)-(C_1-C_6)alkyl, -(C_1-C_4)alkylene-C(=O)-O-(C_1-C_6)alkyl, or -(C_1-C_4)alkylene-C(=O)-OH, wherein two substituents on a carbon ring member of the Y cycloalkyl or heterocyclyl may join to form a 3-7 membered cycloalkyl group or a 3-7 membered heterocyclyl group that comprises 1 to 3 heteroatoms selected from N, O, or S; and further wherein 1 or 2 carbon atom ring members of the 3-7 membered cycloalkyl or the 3-7 membered heterocyclyl group formed from the two substituents on the carbon ring member of the Y cycloalkyl or heterocyclyl may be double bonded to an O atom;

Y' may be absent or is a C_6-C_{10} aryl, a 5-10 membered heteroaryl comprising 1, 2, 3, or 4 heteroatoms independently selected from O, S, or N, or a 3-7 membered heterocyclyl comprising 1, 2, or 3 heteroatoms selected from O, S, or N, wherein the C_6-C_{10} aryl, the 5-10 membered heteroaryl, or the 3-7 membered heterocyclyl Y' groups are unsubstituted or

are optionally substituted with 1, 2, or 3 substituents independently selected from –F, -Cl, -Br, -I, -C≡N, -NO_2, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_1-C_4)alkylene-OH, -NH_2, -NH((C_1-C_4)alkyl), -N((C_1-C_4)alkyl)$_2$, -C(=O)NH_2, -C(=O)NH((C_1-C_4)alkyl), -C(=O)N((C_1-C_4)alkyl)$_2$, -SO_2NH_2, -SO_2NH((C_1-C_4)alkyl), -SO_2N((C_1-C_4)alkyl)$_2$, -NHSO_2-(C_1-C_4)alkyl, -NHC(=O)-(C_1-C_4)alkyl, -SO_2-(C_1-C_6)alkyl, -SO-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-NH-C(=O)-(C_1-C_4)alkyl, -CF_3, -C(=O)-(C_1-C_4)alkyl, -CO_2H, -C(=O)-O-(C_1-C_4)alkyl, -C(=O)NH-(C_1-C_4)alkylene-NH_2, -C(=O)NH-(C_1-C_4)alkylene-NH((C_1-C_4)alkyl), -C(=O)NH-(C_1-C_4)alkylene-N((C_1-C_4)alkyl)$_2$, -C(=O)NH-(C_1-C_4)alkylene-OH, -C(=O)NH-(C_1-C_4)alkylene-CF_3, -C(=O)NH-(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-C(=O)-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-C(=O)-O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-C(=O)-OH, -OH, -O-(C_1-C_6)alkyl, -SH, -S-(C_1-C_6)alkyl, -OCF_3, or -$OCHF_2$;

Y" may be absent or is selected from a C_3-C_{10} cycloalkyl; a 3-10 membered heterocyclyl comprising 1, 2, or 3 heteroatoms selected from N, O, and S; a C_6-C_{10} aryl; or a 5-10 membered heteroaryl comprising 1, 2, 3, or 4 heteroatoms independently selected from N, O, or S; wherein the C_3-C_{10} cycloalkyl and the 3-10 membered heterocyclyl may be monocyclic or bicyclic, and further wherein the C_3-C_{10} cycloalkyl, the 3-10 membered heterocyclyl, the C_6-C_{10} aryl, or the 5-10 membered heteroaryl Y" groups are unsubstituted or are optionally substituted with 1, 2, or 3 substituents independently selected from –F, -Cl, -Br, -I, -C≡N, -NO_2, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_1-C_4)alkylene-OH, -NH_2, -NH((C_1-C_4)alkyl), -N((C_1-C_4)alkyl)$_2$, -C(=O)NH_2, -C(=O)NH((C_1-C_4)alkyl), -C(=O)N((C_1-C_4)alkyl)$_2$, -SO_2NH_2, -SO_2NH((C_1-C_4)alkyl), -SO_2N((C_1-C_4)alkyl)$_2$, -NHSO_2-(C_1-C_4)alkyl, -NHC(=O)-(C_1-C_4)alkyl, -SO_2-(C_1-C_6)alkyl, -SO-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-NH-C(=O)-(C_1-C_4)alkyl, -CF_3, -C(=O)-(C_1-C_4)alkyl, -CO_2H, -C(=O)-O-(C_1-C_4)alkyl, -C(=O)NH-(C_1-C_4)alkylene-NH_2, -C(=O)NH-(C_1-C_4)alkylene-NH((C_1-C_4)alkyl), -C(=O)NH-(C_1-C_4)alkylene-N((C_1-C_4)alkyl)$_2$, -C(=O)NH-(C_1-C_4)alkylene-OH, -C(=O)NH-(C_1-C_4)alkylene-CF_3, -C(=O)NH-(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-C(=O)-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-C(=O)-O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-C(=O)-OH, -OH, -O-(C_1-C_6)alkyl, -SH, -S-(C_1-C_6)alkyl, -OCF_3, or -$OCHF_2$;

W is selected from -$(CR^aR^{a'})_q$-O-$(C_1$-$C_6)$alkyl, -$(CR^aR^{a'})_q$-O-W', -O-$(CR^aR^{a'})_q$-W', -O-$(CR^aR^{a'})_q$-OH, -O-$(CR^aR^{a'})_q$-O-$(C_1$-$C_6)$alkyl, -$(CR^aR^{a'})_q$-O-$(CR^aR^{a'})_q$-OH, -$(CR^aR^{a'})_q$-O-$(CR^aR^{a'})_q$-O-$(C_1$-$C_6)$alkyl, -$(CR^aR^{a'})_q$-SH, -$(CR^aR^{a'})_q$-S-$(C_1$-$C_6)$alkyl, -$(CR^aR^{a'})_q$-S-W', -S-$(CR^aR^{a'})_q$-W', -$(CR^aR^{a'})_q$-S(O)$_2$-$(C_1$-$C_6)$alkyl, -$(CR^aR^{a'})_q$-S(O)$_2$-W', -S(O)$_2$-$(CR^aR^{a'})_q$-W', -$(CR^aR^{a'})_q$-NH_2, -$(CR^aR^{a'})_q$-NH-$(C_1$-$C_6)$alkyl, -$(CR^aR^{a'})_q$-N-$((C_1$-$C_6)$alkyl,$)_2$, -$(CR^aR^{a'})_q$-N^+-$((C_1$-$C_6)$alkyl,$)_3$, -$(CR^aR^{a'})_q$-NH-W', -$(CR^aR^{a'})_q$-NH-$(CR^aR^{a'})_q$-OH, -NH-$(CR^aR^{a'})_q$-W', or -$(CR^aR^{a'})_q$-W';

W' may be absent or is selected from a C_3-C_{10} cycloalkyl; a 3-10 membered heterocyclyl comprising 1, 2, or 3 heteroatoms selected from N, O, and S; a C_6-C_{10} aryl; or a 5-10 membered heteroaryl comprising 1, 2, 3, or 4 heteroatoms independently selected from N, O, or S; wherein the C_3-C_{10} cycloalkyl and the 3-10 membered heterocyclyl may be monocyclic or bicyclic, and further wherein the C_3-C_{10} cycloalkyl, the 3-10 membered heterocyclyl, the C_6-C_{10} aryl, or the 5-10 membered heteroaryl W' groups are unsubstituted or are optionally substituted with 1, 2, 3, or 4 substituents independently selected from –F, -Cl, -Br, -I, -C≡N, -NO_2, -$(C_1$-$C_6)$alkyl, -$(C_2$-$C_6)$alkenyl, -$(C_2$-$C_6)$alkynyl, -$(C_1$-$C_4)$alkylene-OH, -NH_2, -NH$((C_1$-$C_4)$alkyl), -N$((C_1$-$C_4)$alkyl$)_2$, -CH(CF_3)(OH), -$(C_1$-$C_4)$alkylene-NH_2, -$(C_1$-$C_4)$alkylene-NH$((C_1$-$C_4)$alkyl), -$(C_1$-$C_4)$alkylene-NH-$(C_1$-$C_4)$alkylene-CF_3, -$(C_1$-$C_4)$alkylene-N$((C_1$-$C_4)$alkyl$)_2$, -C(=O)NH_2, -C(=O)NH$((C_1$-$C_4)$alkyl), -C(=O)N$((C_1$-$C_4)$alkyl$)_2$, -SO_2NH_2, -SO_2NH$((C_1$-$C_4)$alkyl), -SO_2N$((C_1$-$C_4)$alkyl$)_2$, -NHSO_2-$(C_1$-$C_4)$alkyl, -NHC(=O)-$(C_1$-$C_4)$alkyl, -SO_2-$(C_1$-$C_6)$alkyl, -SO-$(C_1$-$C_4)$alkyl, -$(C_1$-$C_4)$alkylene-NH-C(=O)-$(C_1$-$C_4)$alkyl, -CF_3, -C(=O)-$(C_1$-$C_4)$alkyl, -CO_2H, -C(=O)-O-$(C_1$-$C_4)$alkyl, -C(=O)NH-$(C_1$-$C_4)$alkylene-NH_2, -C(=O)NH-$(C_1$-$C_4)$alkylene-NH$((C_1$-$C_4)$alkyl), -C(=O)NH-$(C_1$-$C_4)$alkylene-N$((C_1$-$C_4)$alkyl$)_2$, -C(=O)NH-$(C_1$-$C_4)$alkylene-OH, -C(=O)NH-$(C_1$-$C_4)$alkylene-CF_3, -C(=O)NH-$(C_1$-$C_4)$alkylene-O-$(C_1$-$C_4)$alkyl, -$(C_1$-$C_4)$alkylene-C(=O)-$(C_1$-$C_4)$alkyl, -$(C_1$-$C_4)$alkylene-C(=O)-O-$(C_1$-$C_4)$alkyl, -$(C_1$-$C_4)$alkylene-C(=O)-OH, -$(C_1$-$C_4)$alkylene-OH, -OH, -O-$(C_1$-$C_6)$alkyl, -SH, -S-$(C_1$-$C_6)$alkyl, -SO_3H, -OCF_3, -$OCHF_2$, or –C(=O)-W"; and further wherein W' may include 0, 1, or 2 =O groups when W' is a C_3-C_{10}

cycloalkyl or a 3-10 membered heterocyclyl, and further wherein the =O groups may be bonded to a ring carbon atom or a ring S atom;

W" may be absent or is selected from a C_3-C_{10} cycloalkyl; a 3-10 membered heterocyclyl comprising 1, 2, or 3 heteroatoms selected from N, O, and S; a C_6-C_{10} aryl; or a 5-10 membered heteroaryl comprising 1, 2, 3, or 4 heteroatoms independently selected from N, O, or S; wherein the C_3-C_{10} cycloalkyl and the 3-10 membered heterocyclyl may be monocyclic or bicyclic, and further wherein the C_3-C_{10} cycloalkyl, the 3-10 membered heterocyclyl, the C_6-C_{10} aryl, or the 5-10 membered heteroaryl W" groups are unsubstituted or are optionally substituted with 1, 2, 3, or 4 substituents independently selected from –F, -Cl, -Br, -I, -C≡N, -NO_2, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -OH, -NH_2, -NH((C_1-C_4)alkyl), -N((C_1-C_4)alkyl)$_2$, -CF_3, -CO_2H, -C(=O)-O-(C_1-C_4)alkyl, -SH, -S-(C_1-C_6)alkyl, -OCF_3, or -$OCHF_2$; and further wherein W" may include 0, 1, or 2 =O groups when W" is a C_3-C_{10} cycloalkyl or a 3-10 membered heterocyclyl, and further wherein the =O groups may be bonded to a ring carbon atom or a ring S atom;

the subscript q is, in each instance, independently selected from 0, 1, 2, 3, or 4;

R^a is, in each instance, independently selected from –H, -CH_3, -CH_2CH_3, -F, -CF_3, or -C≡N;

$R^{a'}$ is, in each instance, independently selected from –H, -CH_3, -CH_2CH_3, -F, -CF_3, or -C≡N; or R^a and $R^{a'}$ may join to form a cyclopropyl ring together with the carbon atom to which they are attached;

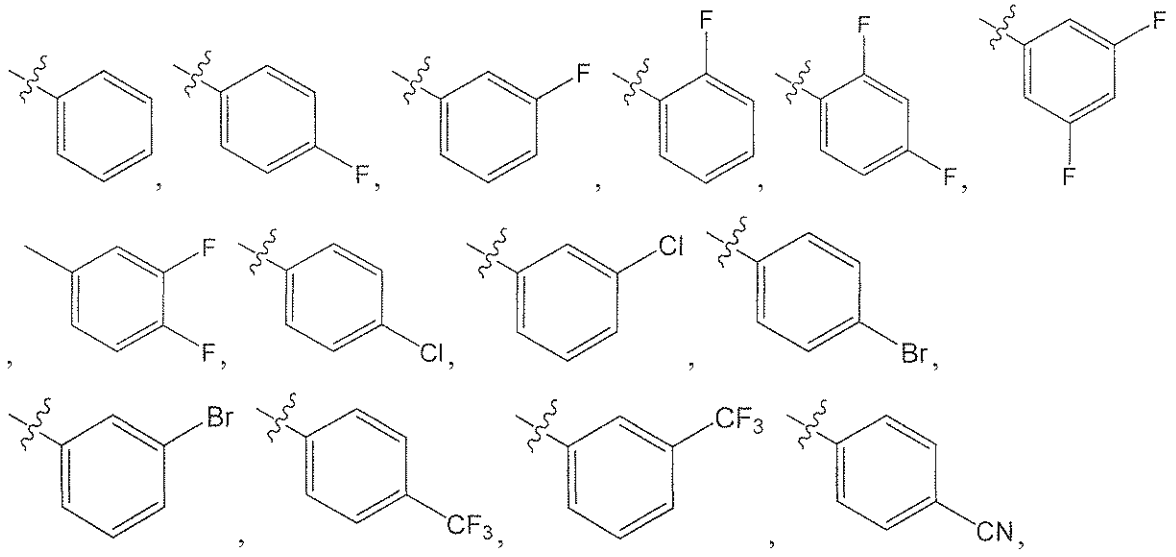
Z is selected from -OMe or -NH-cyclohexyl; or a phenyl, pyridyl, benzothiophenyl, thiazolyl, pyradizinyl, pyrimidinyl, indolyl, cyclohexyl, morpholinyl, pyrrolidinyl, piperazinyl, or piperidinyl group; wherein the –NH-cyclohexyl, phenyl, pyridyl, benzothiophenyl, thiazolyl, pyradizinyl, pyrimidinyl, indolyl, cyclohexyl, morpholinyl, pyrrolidinyl, piperazinyl, or piperidinyl group is unsubstituted or is optionally substituted with 1, 2, or 3 substituents independently selected from –F, -Cl, -Br, -I, -C≡N, -NO_2, -CF_3, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -(C_1-C_4)alkylene-OH, -NH_2, -NH((C_1-C_6)alkyl), -N((C_1-C_6)alkyl)$_2$, -C(=O)NH_2, -C(=O)NH((C_1-C_6)alkyl), -C(=O)N((C_1-C_6)alkyl)$_2$, -SO_2NH_2, -SO_2NH((C_1-C_6)alkyl), -SO_2N((C_1-C_6)alkyl)$_2$, -SO_2NH((C_2-C_6)alkenyl), -SO_2NH((C_2-C_6)alkynyl), -SO_2NH-(C_1-C_4)alkylene-OH, -SO_2NH-(C_1-C_4)alkylene-O-(C_1-C_6)alkyl, -$NHSO_2$-(C_1-C_6)alkyl, -NHC(=O)-(C_1-C_6)alkyl, -SO_2-(C_1-

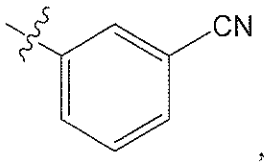
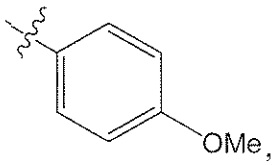
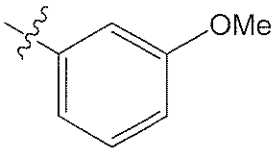
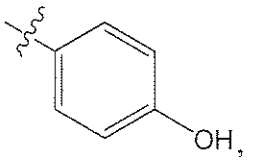
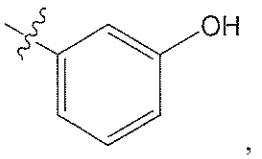
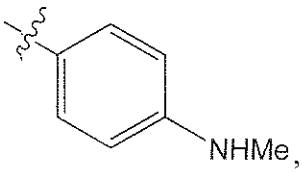
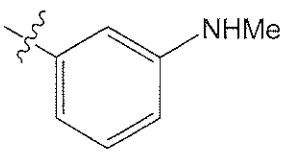
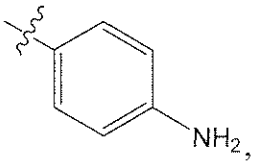
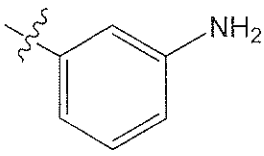
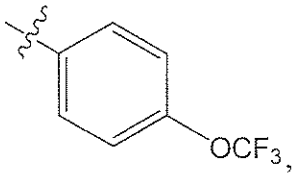
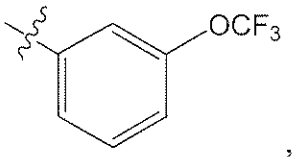
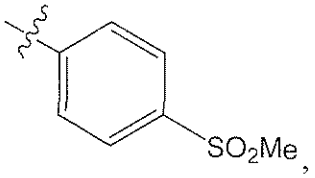
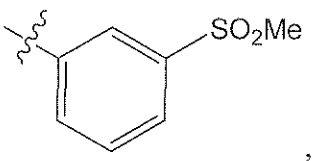
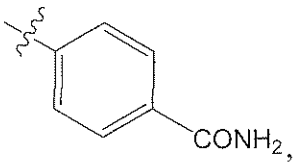
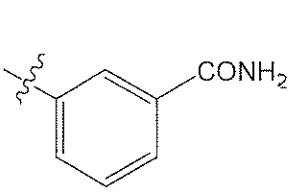
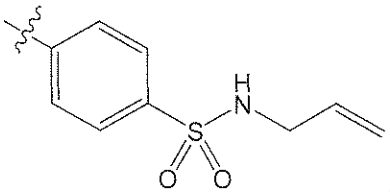
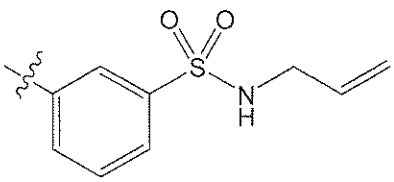
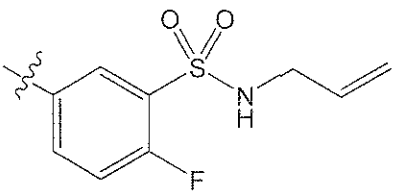
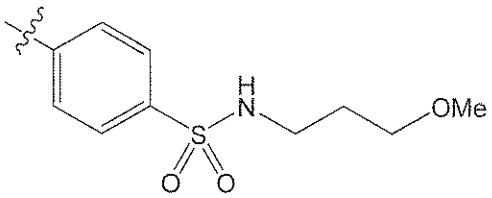
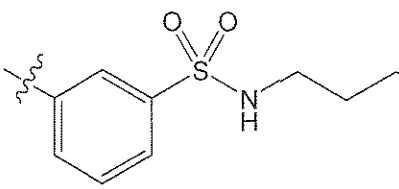
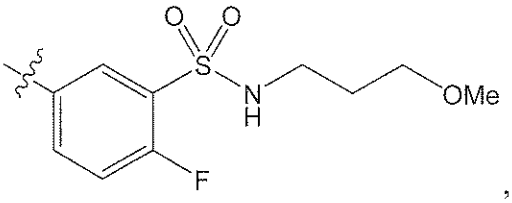
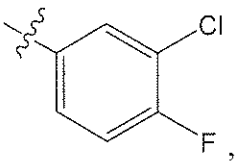
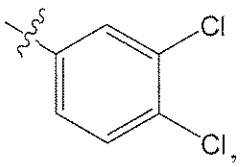
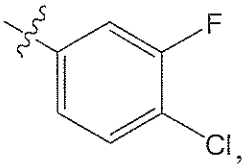
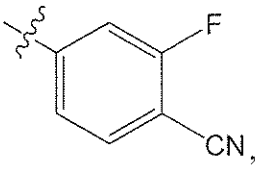
C_6)alkyl, -SO-(C_1-C_6)alkyl, -(C_1-C_4)alkylene-NH-C(=O)-(C_1-C_6)alkyl, -C(=O)-(C_1-C_6)alkyl, -CO_2H, -C(=O)-O-(C_1-C_6)alkyl, -C(=O)NH-(C_1-C_4)alkylene-NH_2, -C(=O)NH-(C_1-C_4)alkylene-NH((C_1-C_6)alkyl), -C(=O)NH-(C_1-C_4)alkylene-N((C_1-C_6)alkyl)$_2$, -(C_1-C_4)alkylene-C(=O)-(C_1-C_6)alkyl, -(C_1-C_4)alkylene-C(=O)-O-(C_1-C_6)alkyl, -(C_1-C_4)alkylene-C(=O)-OH, -OH, -O-(C_1-C_6)alkyl, -SH, -S-(C_1-C_6)alkyl, -OCF_3, or -$OCHF_2$.

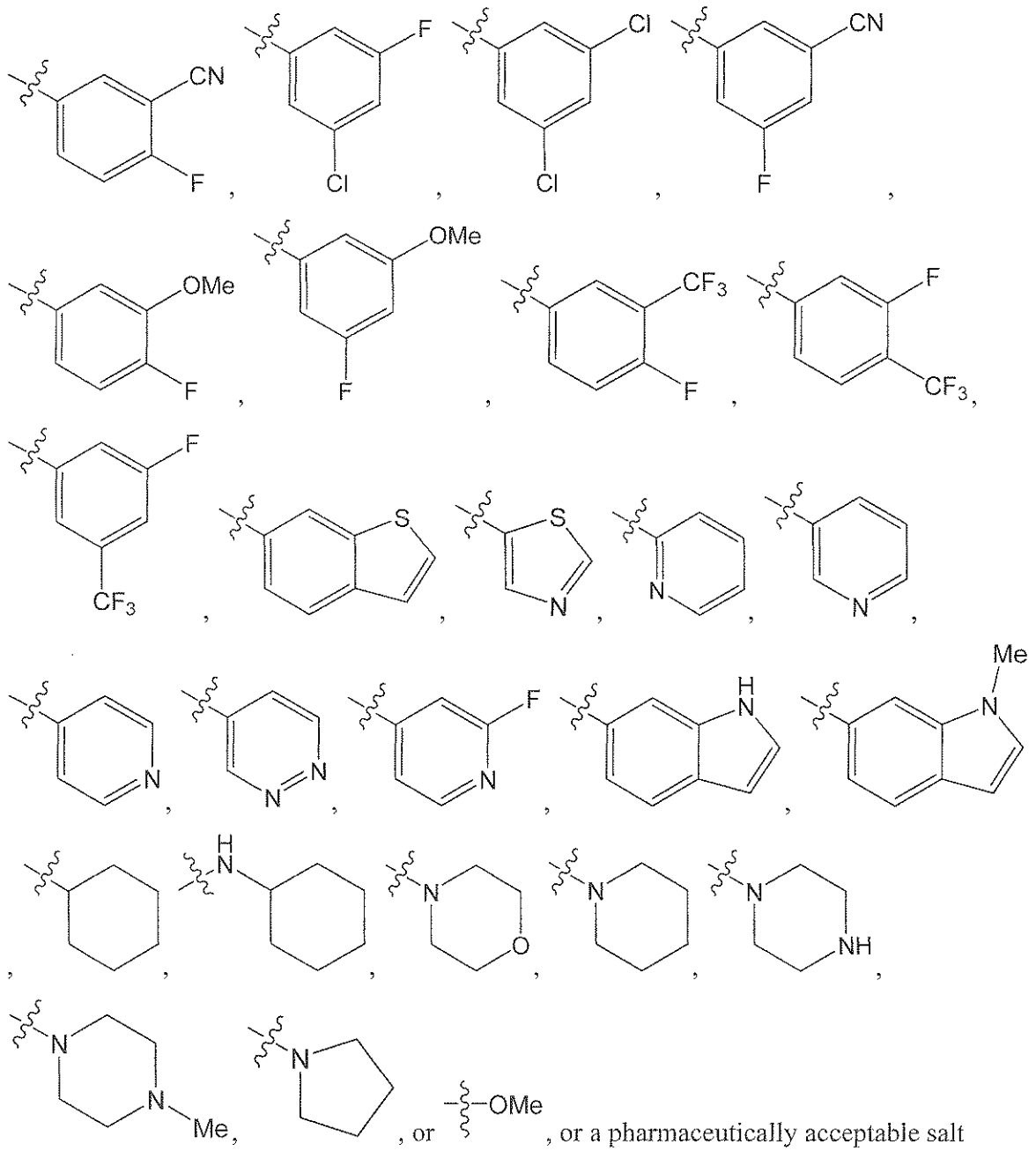
2. The compound of Claim 1, wherein Z is an unsubstituted or substituted phenyl, pyridyl, benzothiophenyl, thiazolyl, pyradizinyl, pyrimidinyl, indolyl, cyclohexyl, morpholinyl, pyrrolidinyl, piperazinyl, or piperidinyl group, or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, or a stereoisomer of any of the foregoing.

3. The compound of Claim 1, wherein Z is an unsubstituted or substituted phenyl or pyridyl, or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, or a stereoisomer of any of the foregoing.

4. The compound of Claim 1, wherein Z is selected from

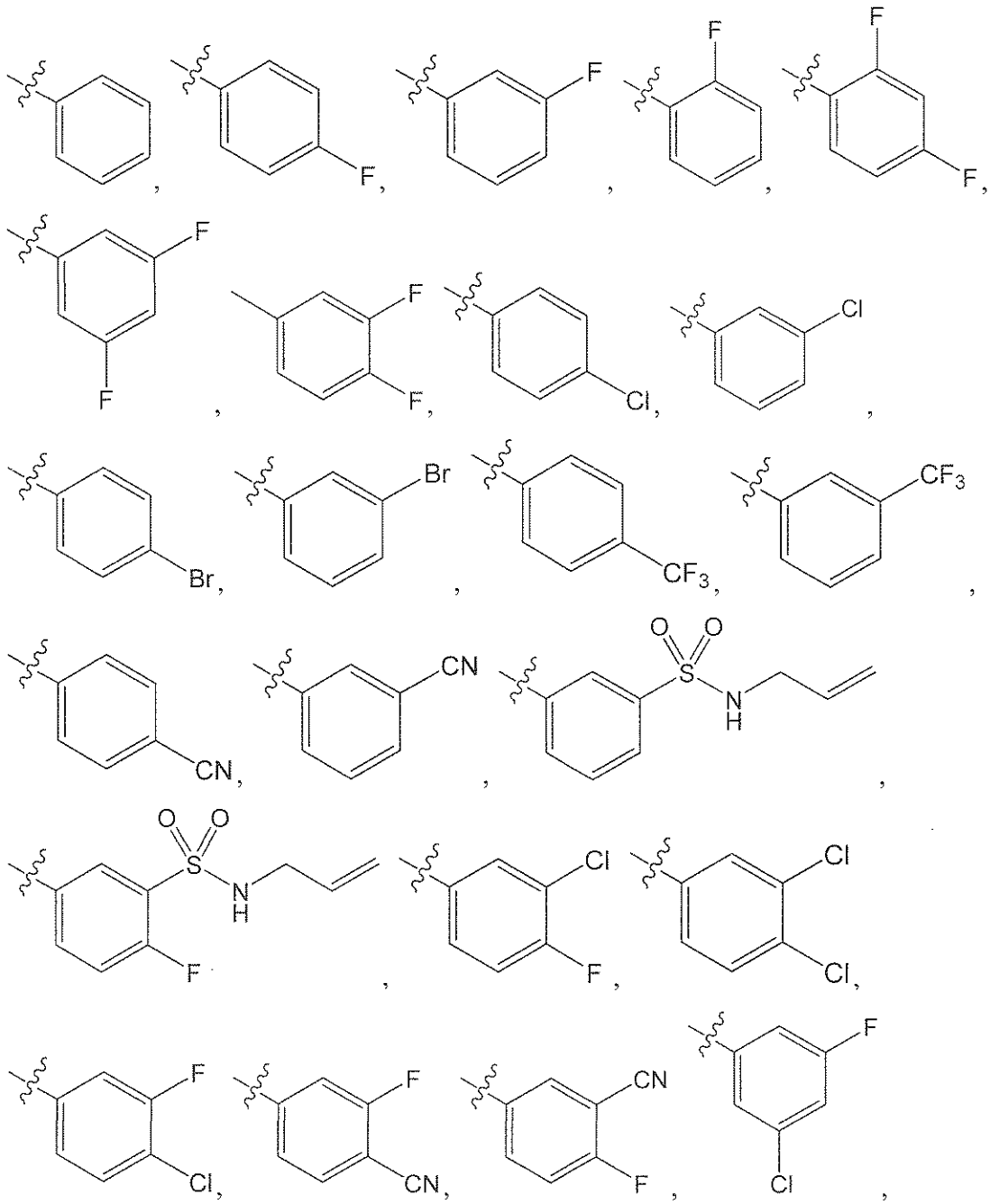


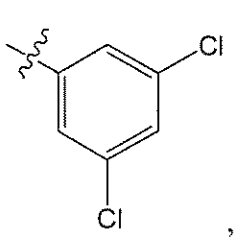




























thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, or a stereoisomer of any of the foregoing, wherein the symbol ~~~, when drawn across a bond, indicates the point of attachment to the rest of the molecule.

5. The compound of Claim 1, wherein Z is selected from





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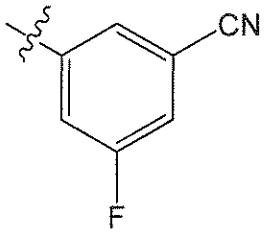

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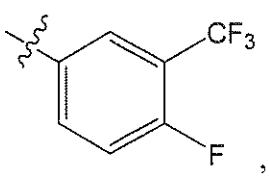

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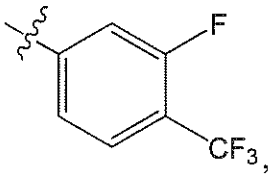

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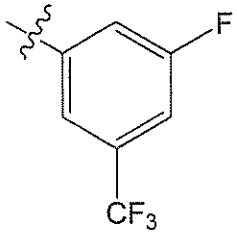

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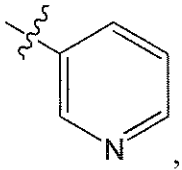

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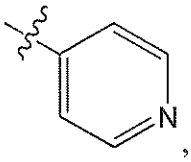
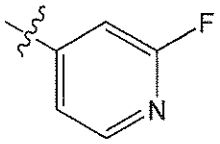


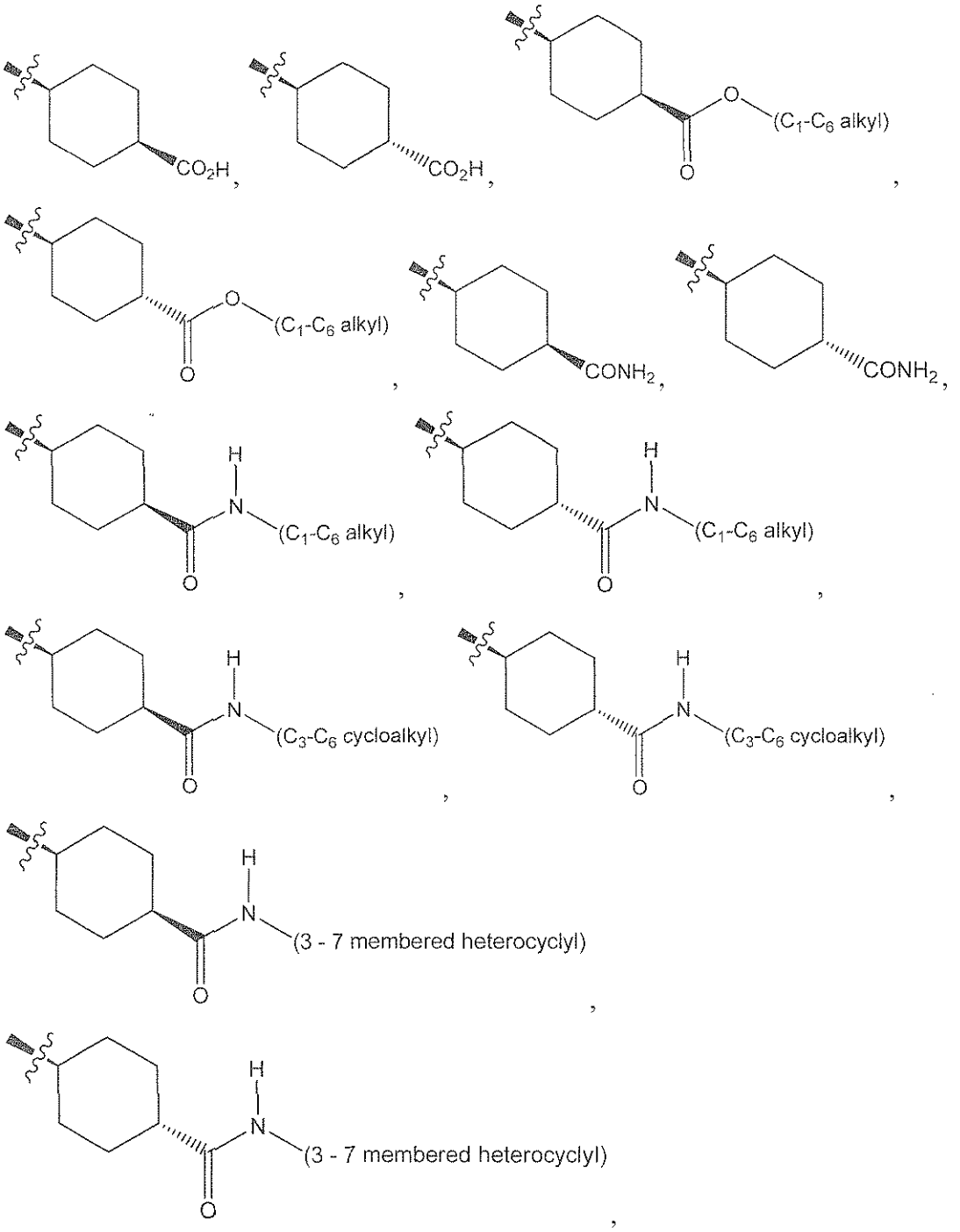
, or


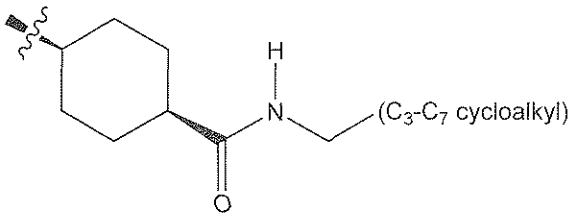
, or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, or a stereoisomer of any of the foregoing, wherein the symbol ~~~, when drawn across a bond, indicates the point of attachment to the rest of the molecule.

6. The compound of Claim 1, wherein Y is substituted cycloheptyl, cyclohexyl, cyclopentyl, cyclobutyl, piperidinyl, pyrrolidinyl, azetidinyl, adamantyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[4.1.1]octyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, or bicyclo[2.1.1]hexyl, or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, or a stereoisomer of any of the foregoing.

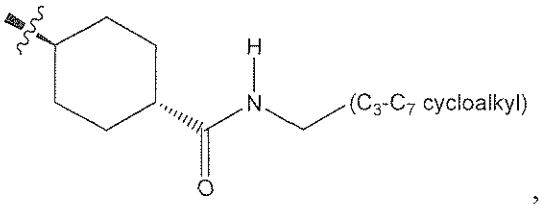
7. The compound of Claim 6, wherein Y is substituted cyclohexyl, or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, or a stereoisomer of any of the foregoing.

8. The compound of Claim 1, wherein Y is selected from

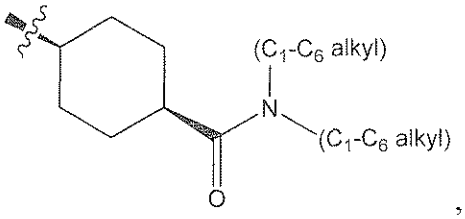



H
N
(C_3-C_7 cycloalkyl)
O

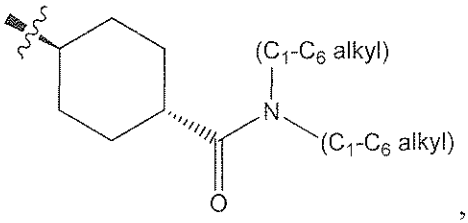
,


H
N
(C_3-C_7 cycloalkyl)
O

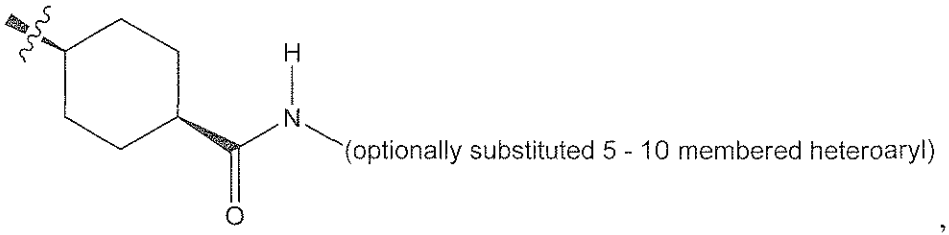
,


(C_1-C_6 alkyl)
N
(C_1-C_6 alkyl)
O

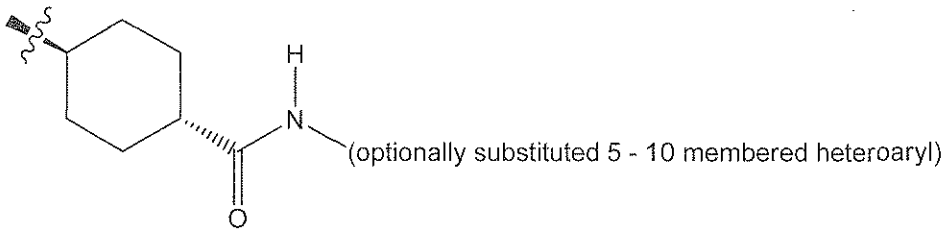
,


(C_1-C_6 alkyl)
N
(C_1-C_6 alkyl)
O

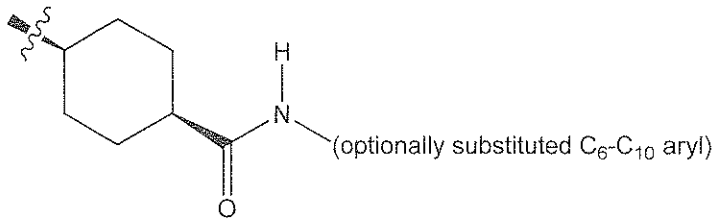
,


H
N
(optionally substituted 5 - 10 membered heteroaryl)
O

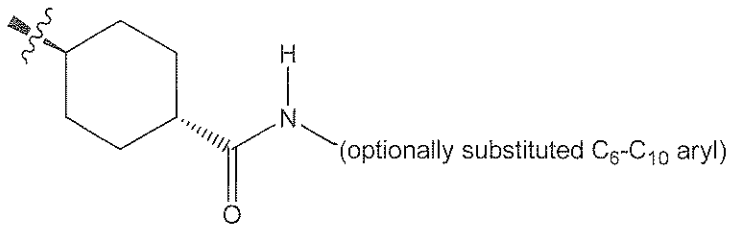
,


H
N
(optionally substituted 5 - 10 membered heteroaryl)
O

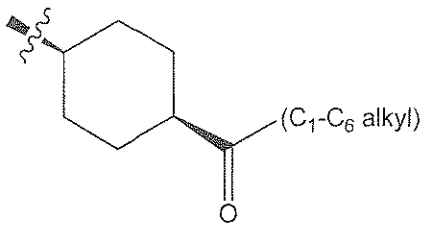
,

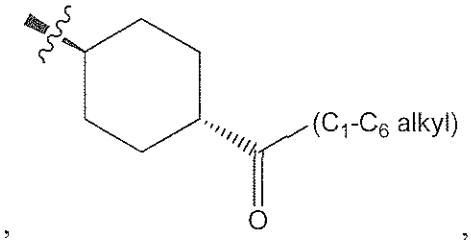

H
N
(optionally substituted C_6-C_{10} aryl)
O

,

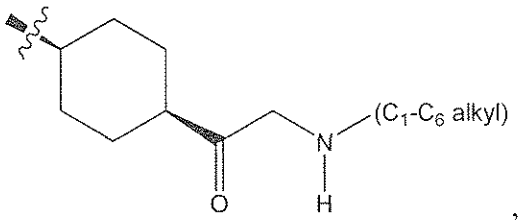

H
N
(optionally substituted C_6-C_{10} aryl)
O

,

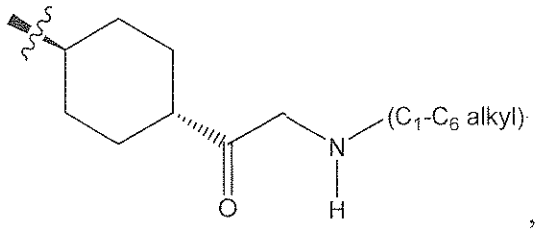

(C_1-C_6 alkyl)
O


(C1-C6 alkyl)
O

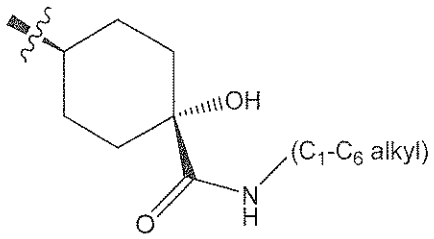
,


(C1-C6 alkyl)
N
H
O

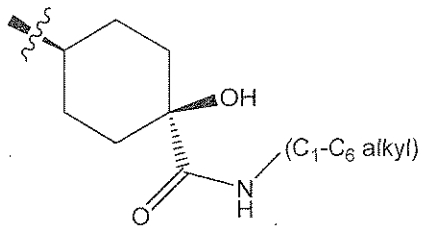
,


(C1-C6 alkyl)
N
H
O

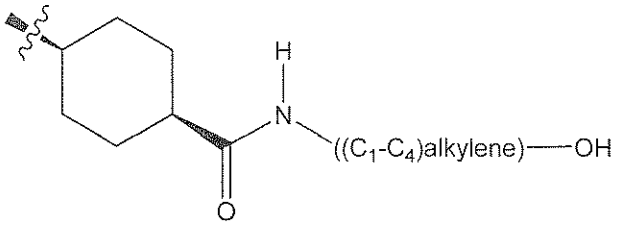
,


OH
(C1-C6 alkyl)
N
H
O

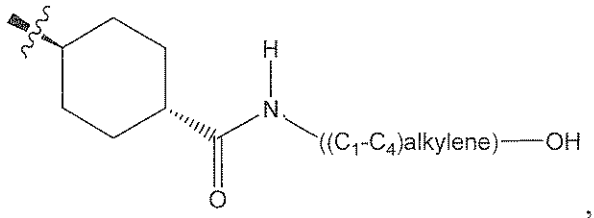
,


OH
(C1-C6 alkyl)
N
H
O

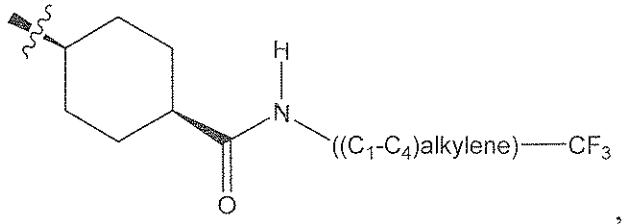
,


H
N
((C1-C4)alkylene)—OH
O

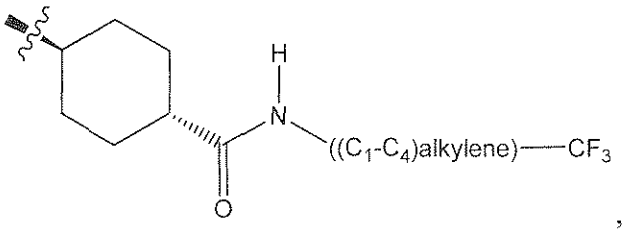
,


H
N
((C1-C4)alkylene)—OH
O

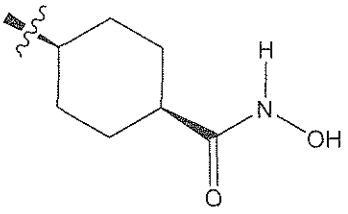
,


H
N
((C1-C4)alkylene)—CF3
O

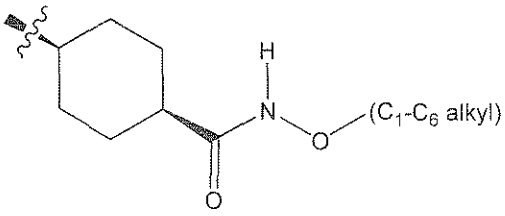
,


H
N
((C1-C4)alkylene)—CF3
O

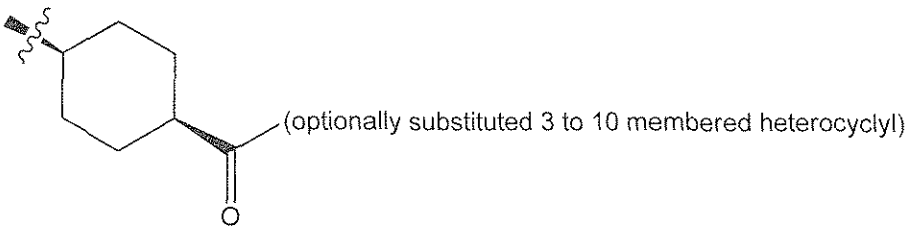
,


H
N
OH
O

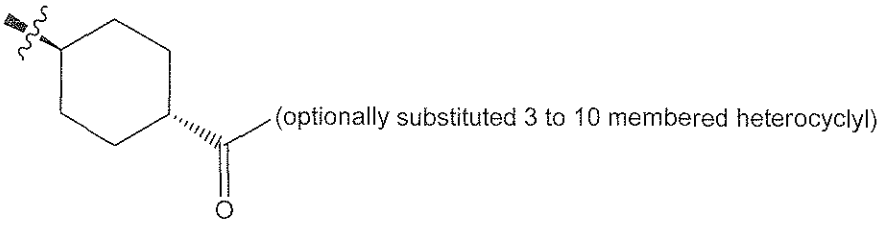
,


H
N
O
(C1-C6 alkyl)
O

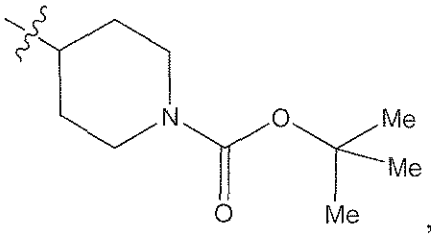
,


(optionally substituted 3 to 10 membered heterocyclyl)
O

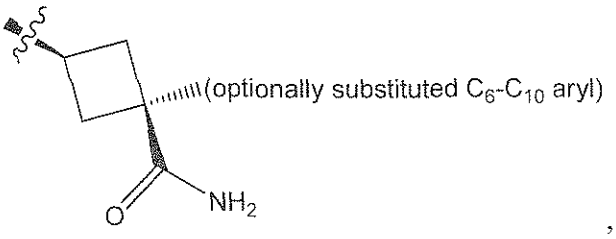
,


(optionally substituted 3 to 10 membered heterocyclyl)
O

,


N
O
Me
Me
O
Me

,



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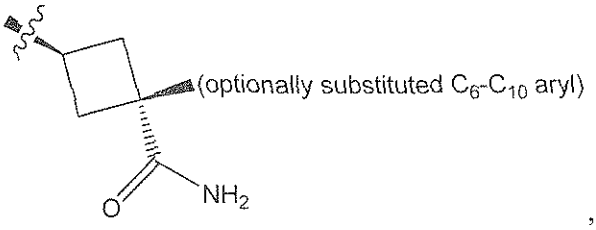
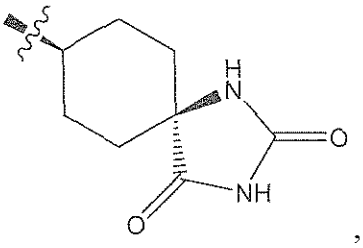
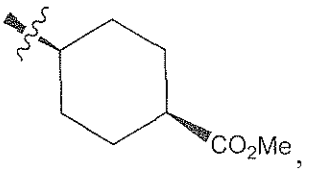


, or



, or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, or a stereoisomer of any of the foregoing, wherein the symbol ~~~, when drawn across a bond, indicates the point of attachment to the rest of the molecule.

9. The compound of Claim 1, wherein Y is selected from



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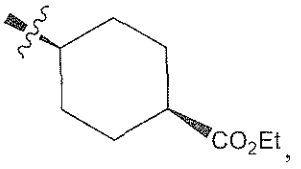

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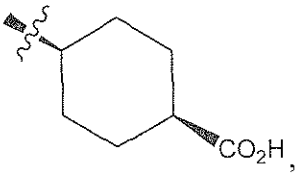

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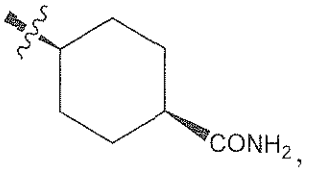

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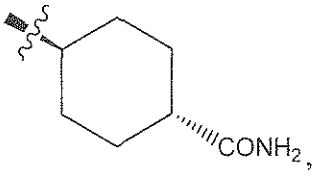

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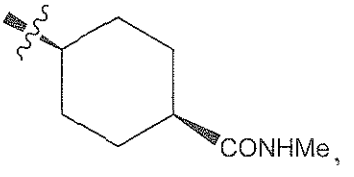

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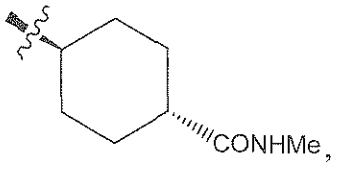

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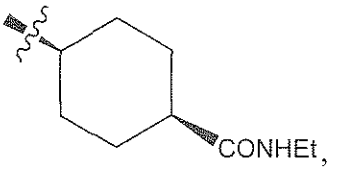

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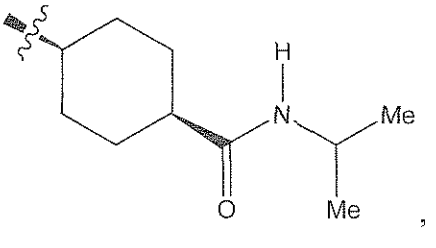

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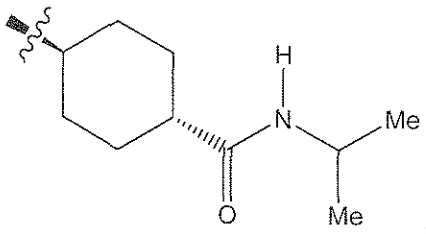
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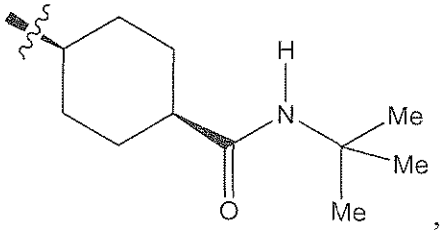
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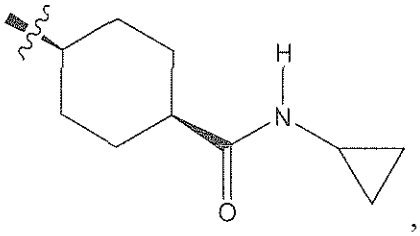
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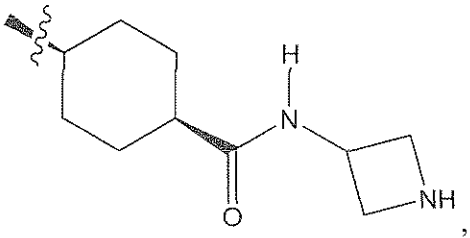
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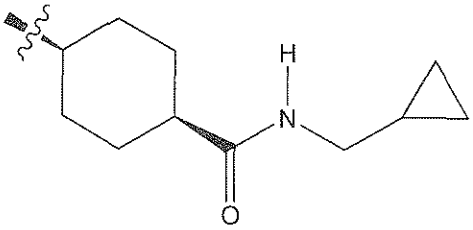
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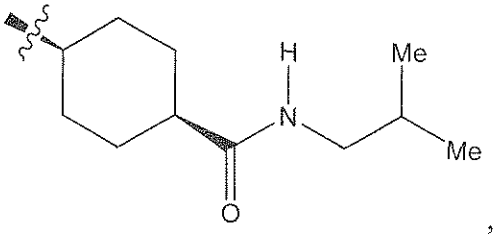
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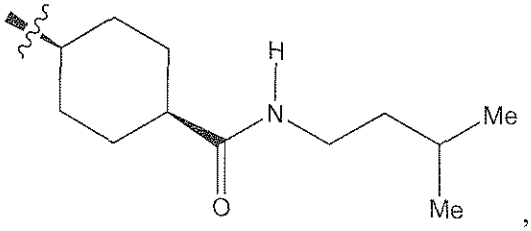
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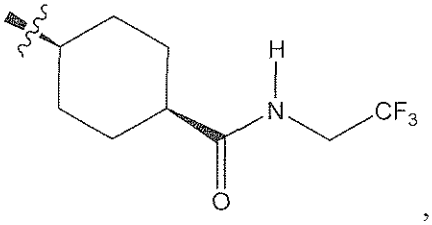
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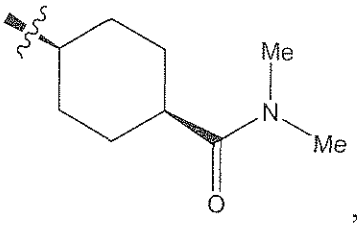
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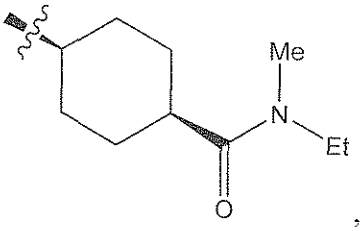
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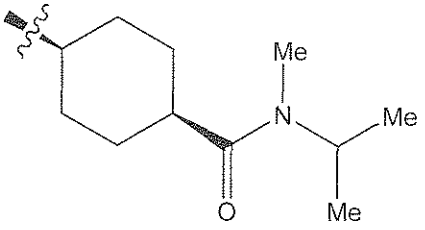
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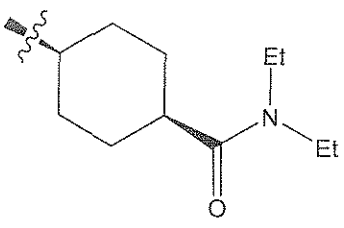
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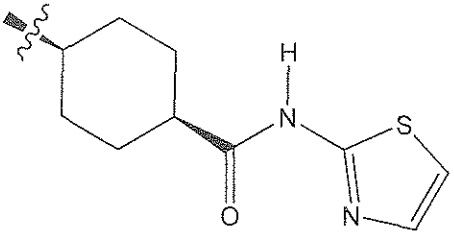
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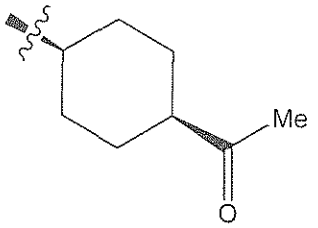
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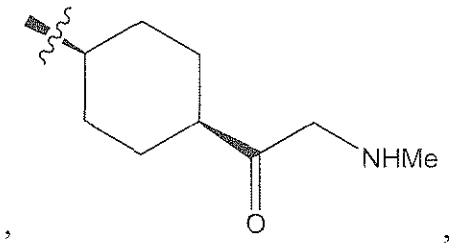
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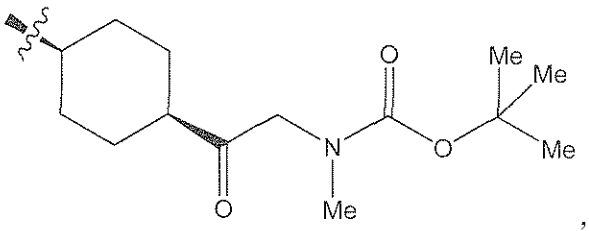
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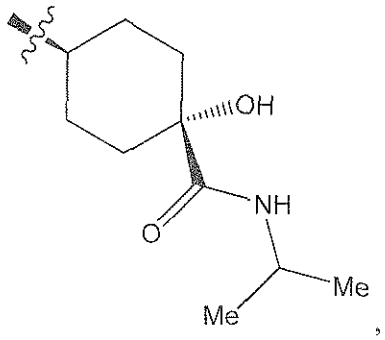
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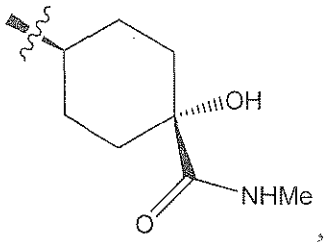
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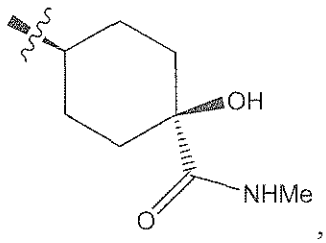
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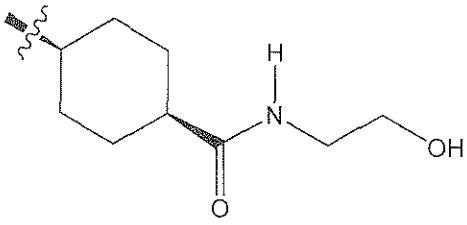
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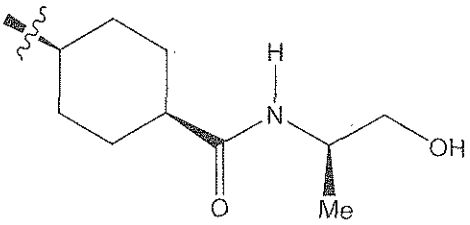
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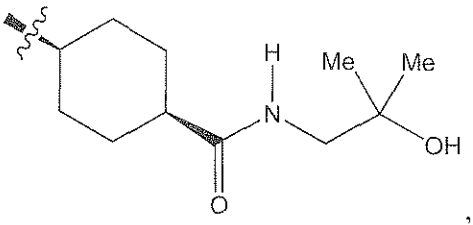
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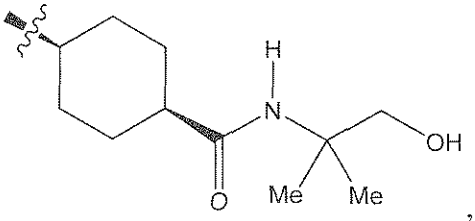
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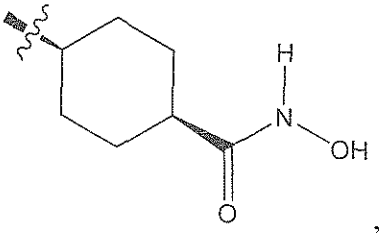
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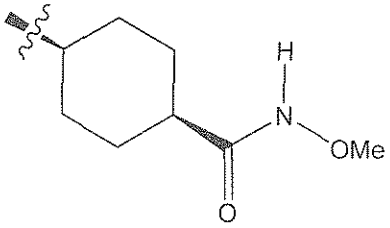
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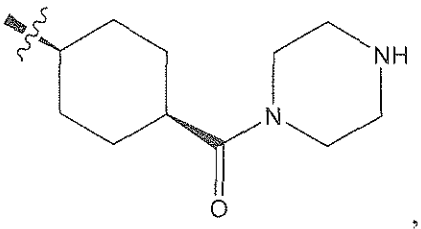
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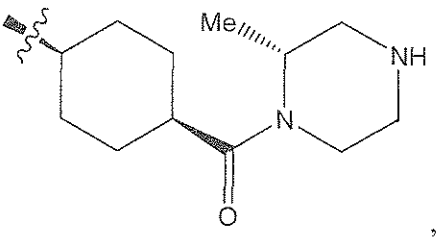
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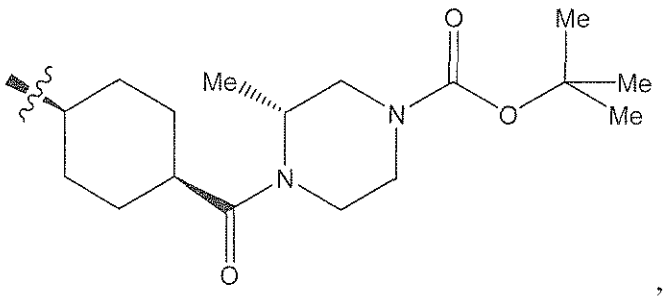

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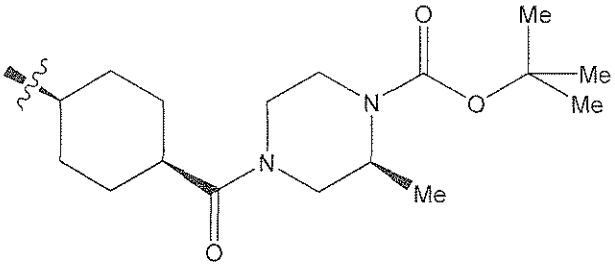

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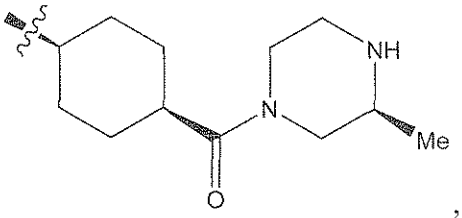

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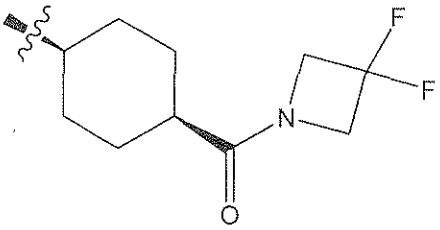

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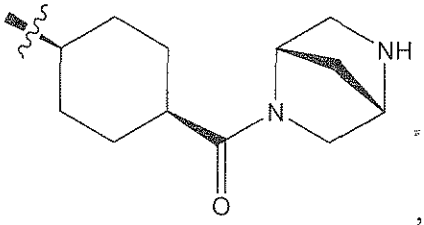

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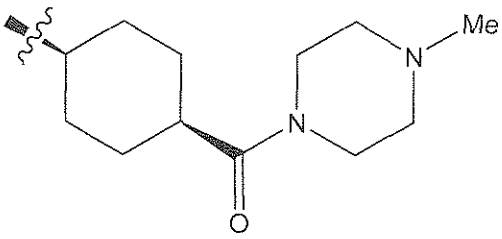

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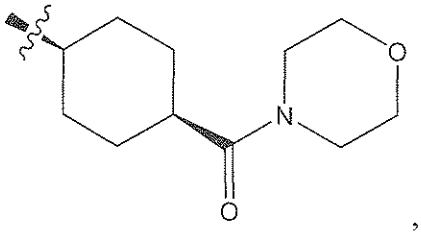

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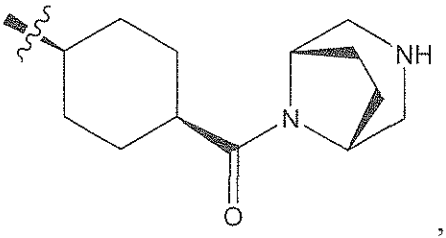

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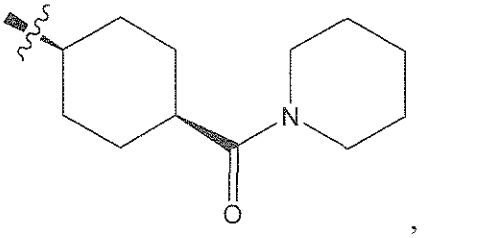

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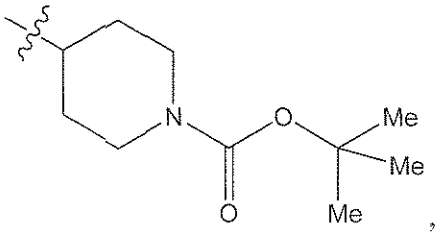

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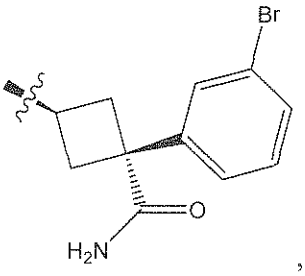

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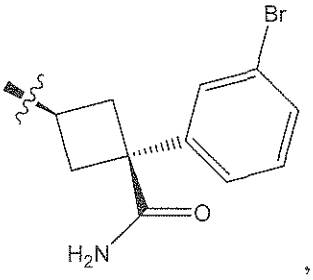

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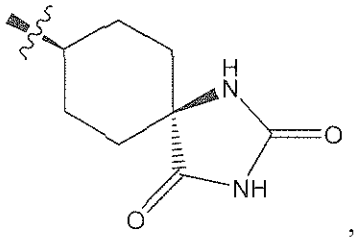
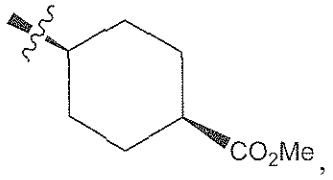


, or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, or a stereoisomer of any of the foregoing, wherein the symbol ~~~, when drawn across a bond, indicates the point of attachment to the rest of the molecule.

10. The compound of Claim 1, wherein Y is selected from



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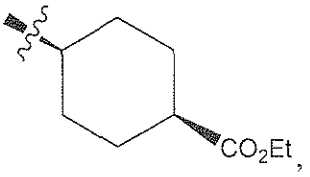

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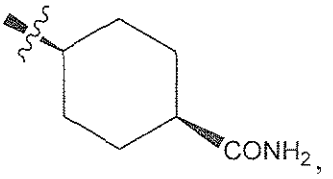

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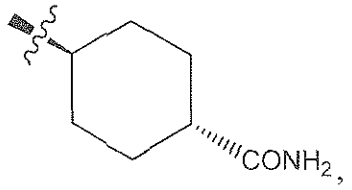

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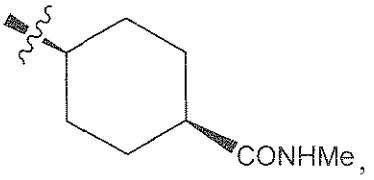

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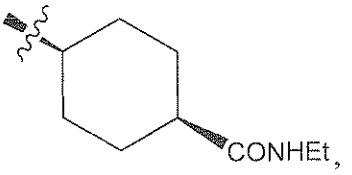

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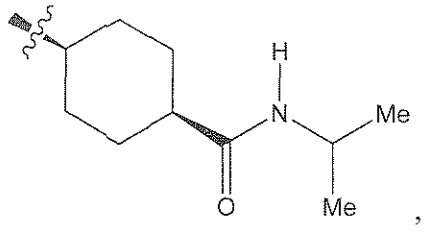

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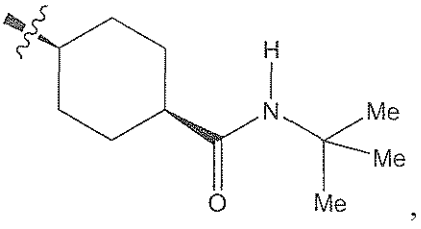

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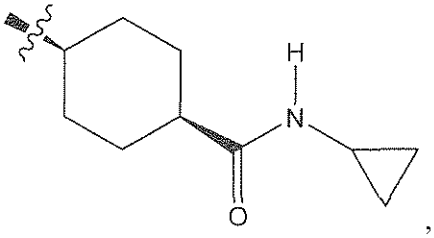
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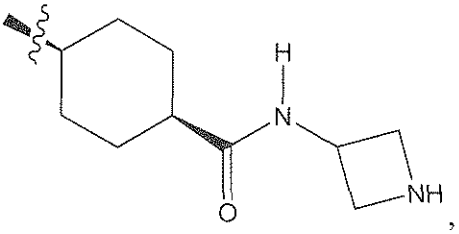
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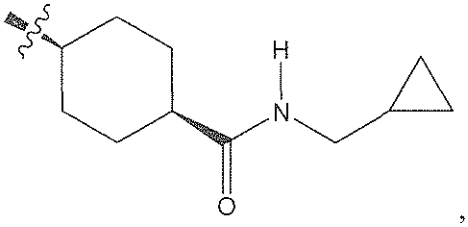
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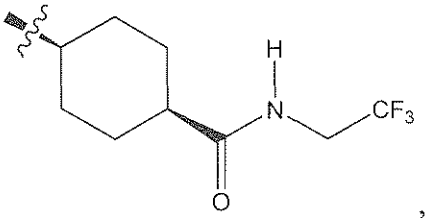
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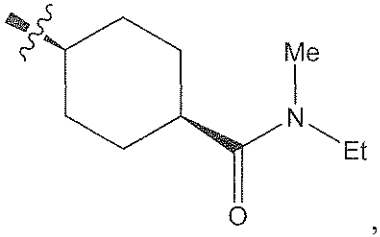
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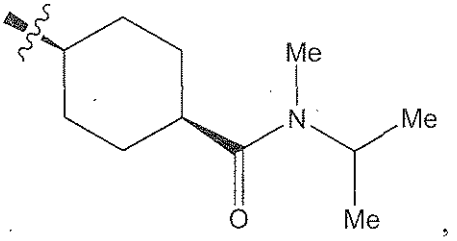
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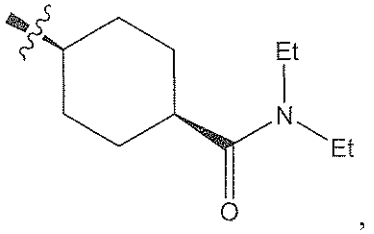
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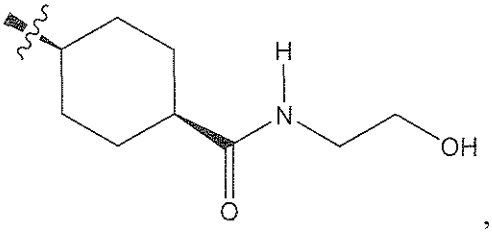
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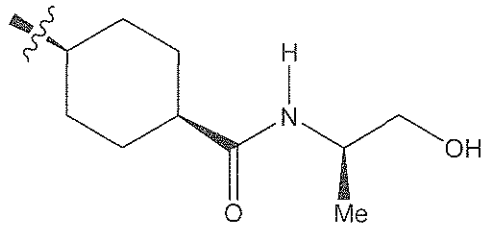
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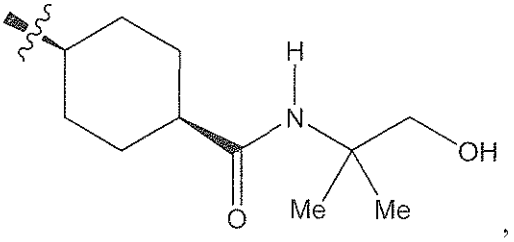
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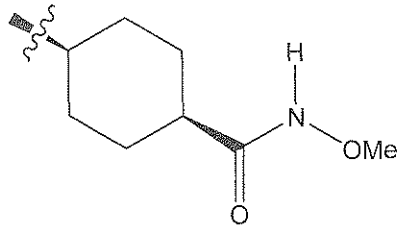
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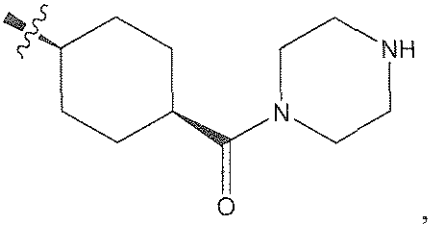
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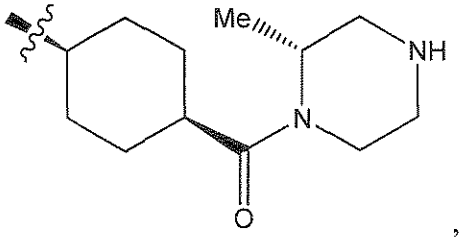

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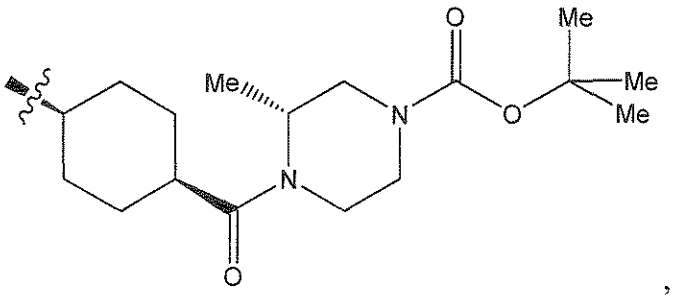

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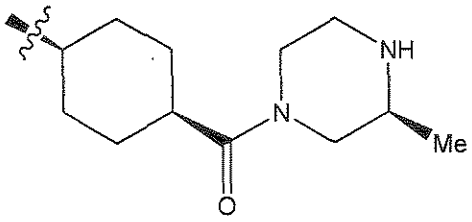

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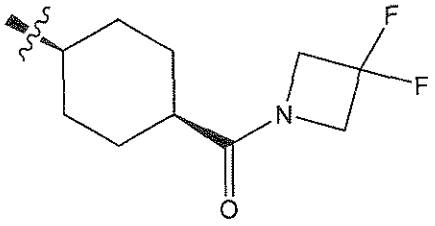

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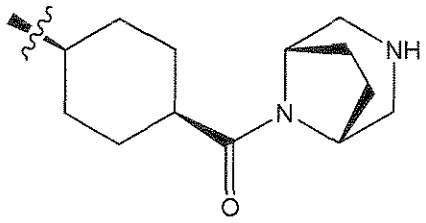

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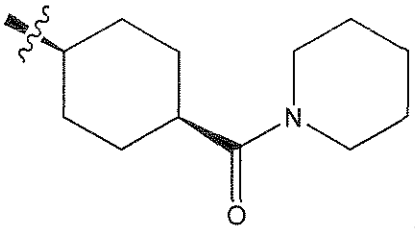
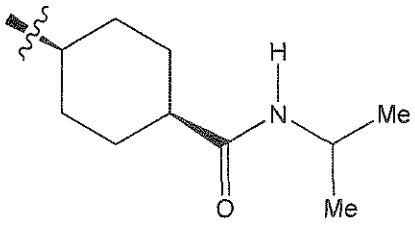


, or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, or a stereoisomer of any of the foregoing, wherein the symbol ∿∿∿, when drawn across a bond, indicates the point of attachment to the rest of the molecule.

11. The compound of claim 10, wherein Y is



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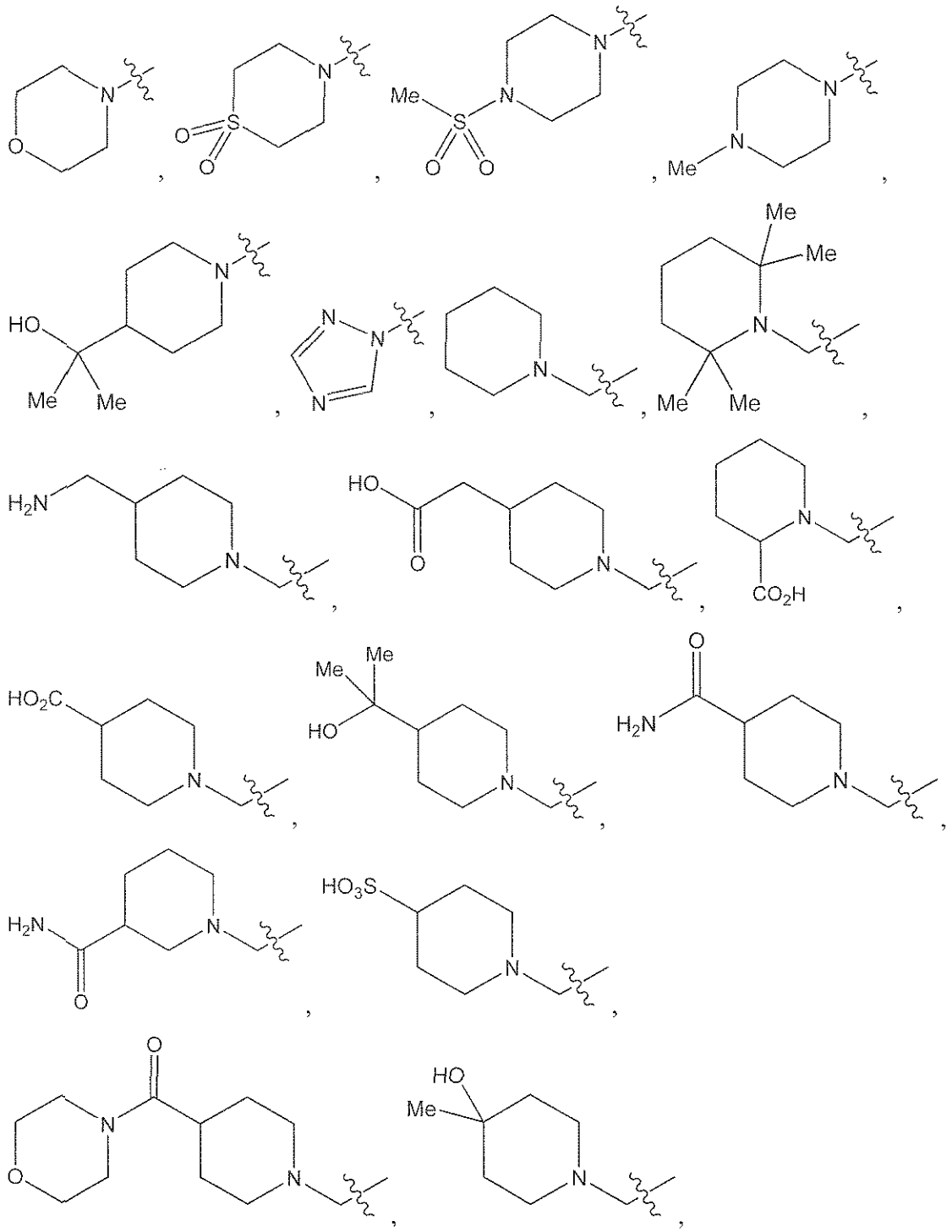
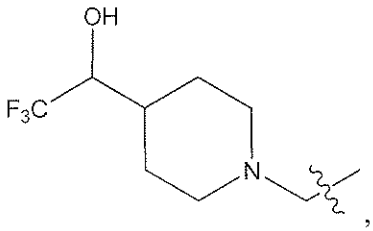
or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, or a stereoisomer of any of the foregoing, wherein the symbol ∿∿∿, when drawn across a bond, indicates the point of attachment to the rest of the molecule.

12. The compound of Claim 1, wherein W is selected from $-CH_2OCH_3$, $-CH_2OCH_2CH_2OH$, $-CH_2OCH_2CH_2OCH_3$, $-OCH_2CH_2OH$, $-OCH_2CH_2OMe$, -W', $-CH_2W'$, -OW', $-OCH_2W'$, $-OCH_2CH_2W'$, $-OCH_2CH_2CH_2W'$, -NHW', $-NHCH_2W'$, $-NHCH_2CH_2W'$, $-NHCH_2CH_2CH_2W'$, or -W'-C(=O)-W"; wherein W', if present, is selected from a 3-10 membered heterocyclyl comprising 1 or 2 heteroatoms selected from N, O, and S; a C_6-C_{10} aryl; or a 5-10 membered heteroaryl comprising 1, 2, 3, or 4 heteroatoms independently selected from N, O, or S; wherein the 3-10 membered heterocyclyl W' group may be monocyclic or bicyclic, and further wherein the 3-10 membered heterocyclyl, the C_6-C_{10} aryl, or the 5-10 membered heteroaryl W' groups are unsubstituted or are substituted with 1, 2, 3, or 4 substituents independently selected from –F, -Cl, -Br, -(C_1-C_6)alkyl, $-CH(CF_3)(OH)$, -(C_1-C_4)alkylene-NH_2, -(C_1-C_4)alkylene-NH-(C_1-C_4)alkylene-CF_3, $-C(=O)NH_2$, $-SO_2$-(C_1-C_6)alkyl, $-CF_3$, $-CO_2H$, -(C_1-C_4)alkylene-C(=O)-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-C(=O)-O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-C(=O)-OH, -(C_1-C_4)alkylene-OH, -OH, -O-(C_1-C_6)alkyl, or $-SO_3H$; and further wherein W' may include 0, 1, or 2 =O groups when W' is a 3-10 membered heterocyclyl, and further wherein the =O groups may be bonded to a ring carbon atom or a ring S atom; and further wherein W", if present, is a 3-10 membered heterocyclyl comprising 1, 2, or 3 heteroatoms selected from N, O, and S, wherein the 3-10 membered heterocyclyl W" group may be monocyclic or bicyclic, and further wherein the 3-10 membered heterocyclyl W" group is unsubstituted or is optionally substituted with 1, 2, 3, or 4 substituents independently selected from –F, -Cl, -Br, -I, -C≡N, $-NO_2$, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, -OH, $-NH_2$, -NH((C_1-C_4)alkyl), -N((C_1-C_4)alkyl)$_2$, $-CF_3$, $-CO_2H$, -C(=O)-O-(C_1-C_4)alkyl, -SH, -S-(C_1-C_6)alkyl, $-OCF_3$, or $-OCHF_2$, or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, or a stereoisomer of any of the foregoing.

13. The compound of Claim 1, wherein W is selected from -OMe, -SO_2Me, -CH_2OMe, -OCH_2CH_2OH, -OCH_2CH_2OMe, or a group selected from

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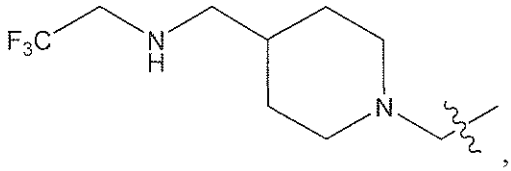
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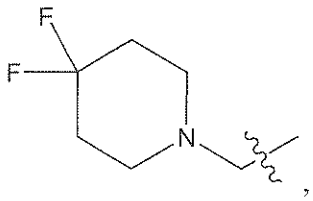
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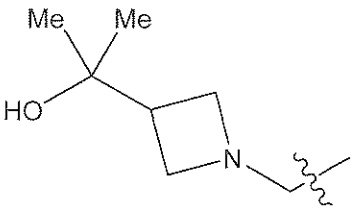
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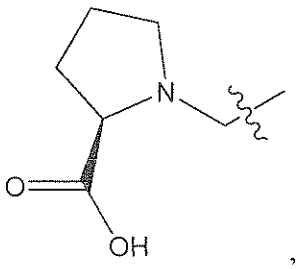
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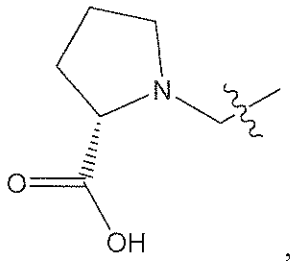
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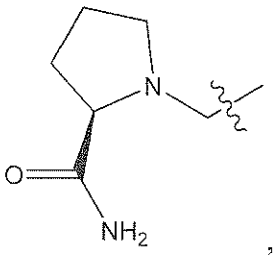
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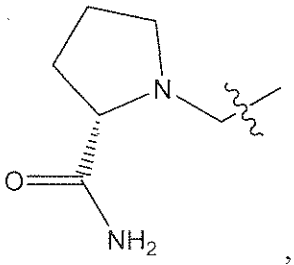
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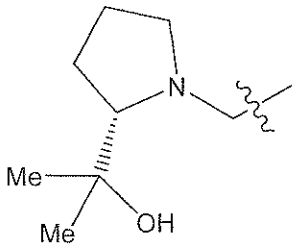
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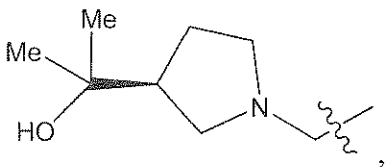
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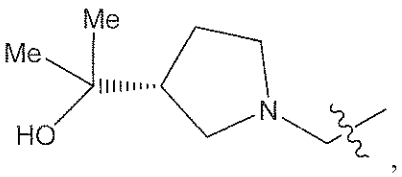
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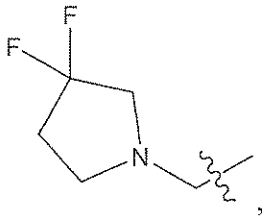
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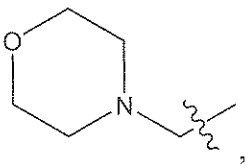
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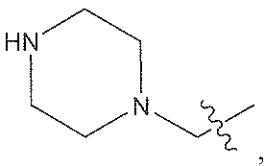
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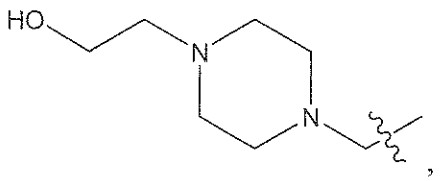
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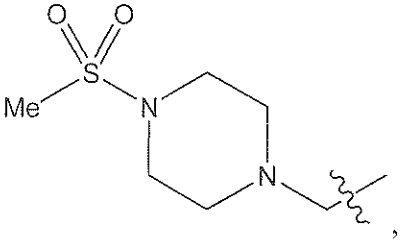
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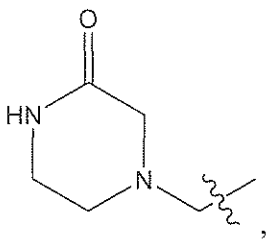
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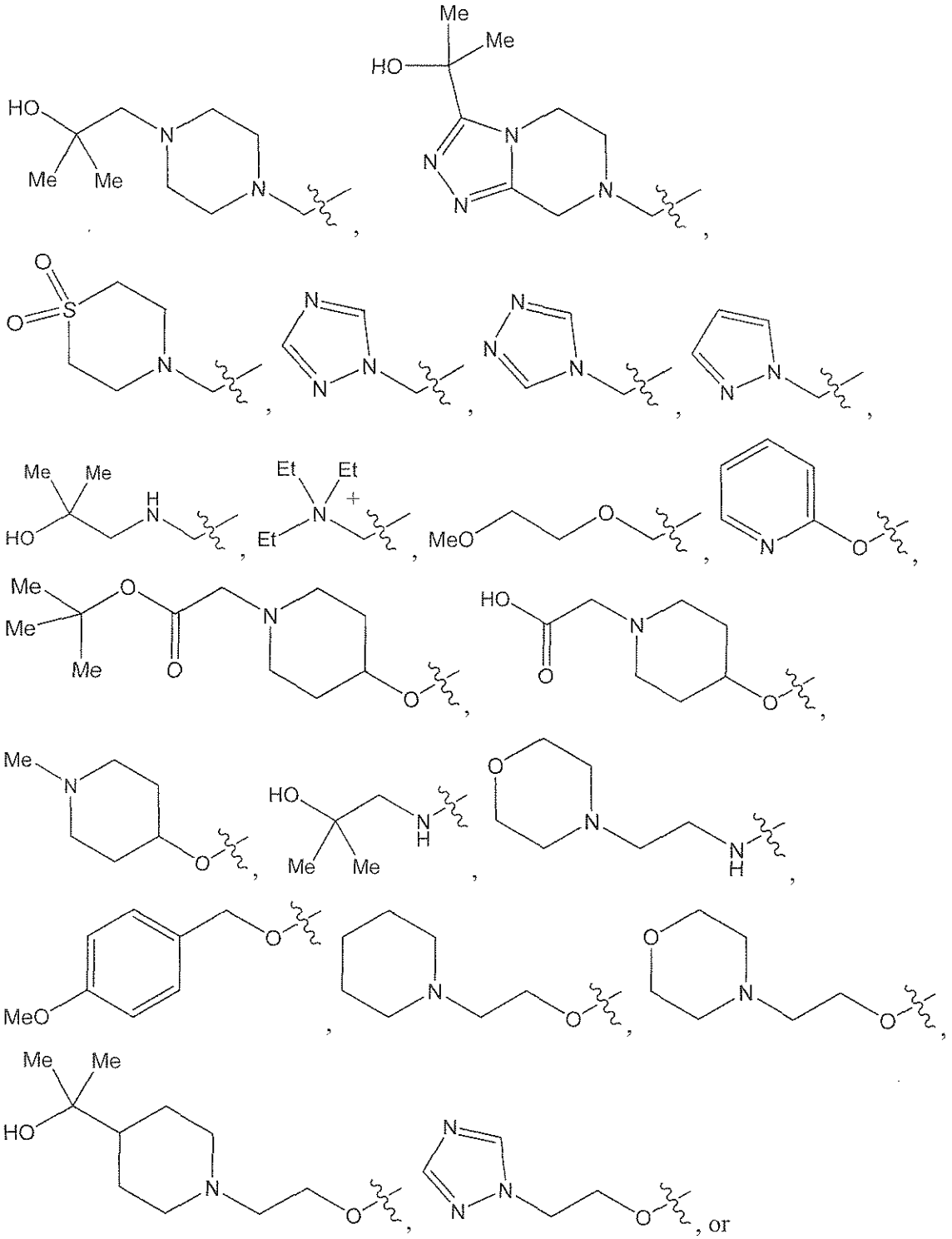
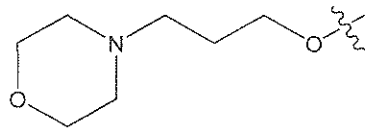
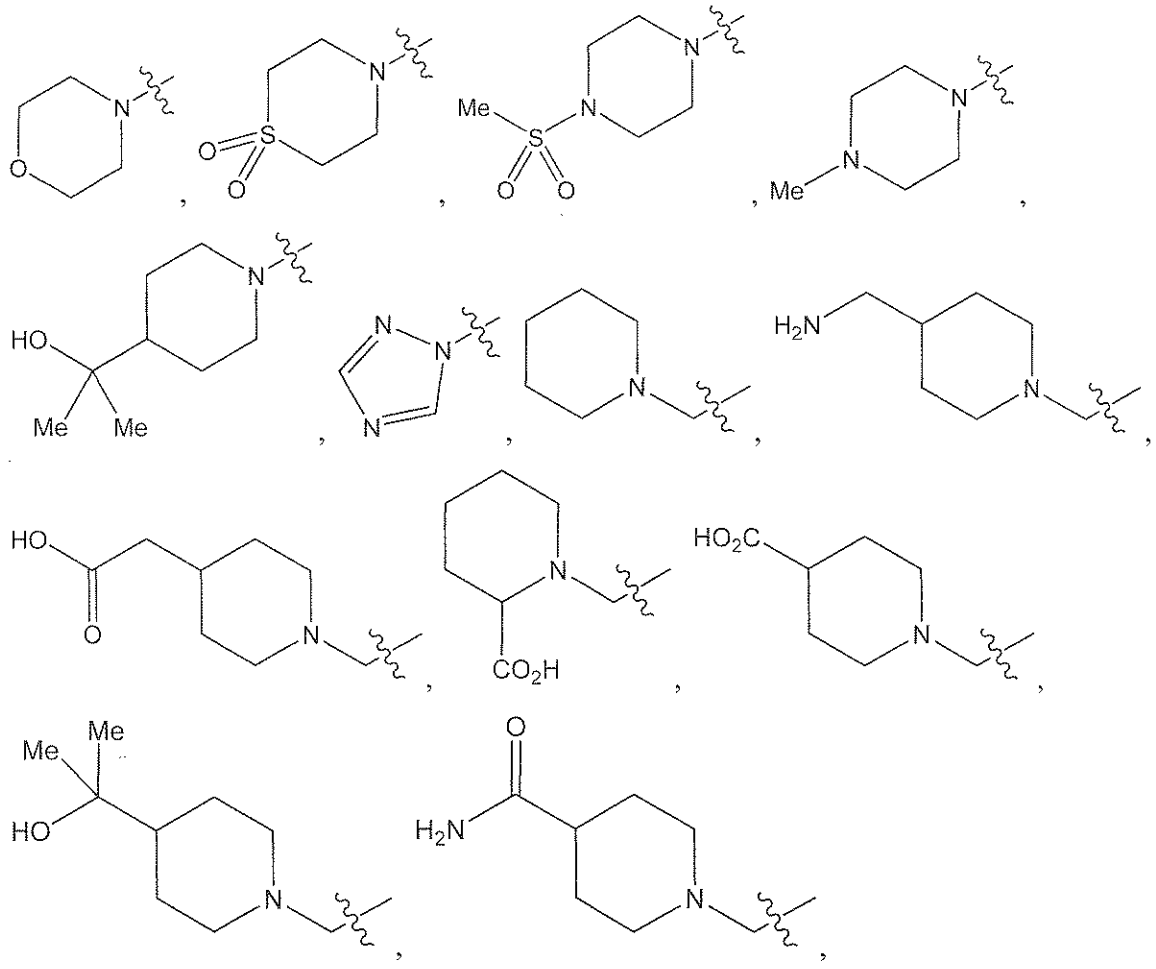
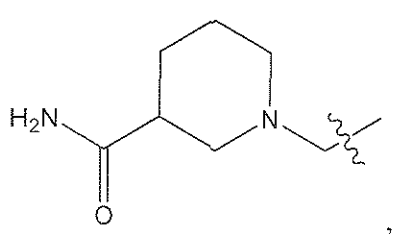




, or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, or a stereoisomer of any of the foregoing, wherein the symbol ∿∿∿, when drawn across a bond, indicates the point of attachment to the rest of the molecule.

14. The compound of Claim 1, wherein W is selected from $-SO_2Me$, $-CH_2OMe$, $-OCH_2CH_2OH$, $-OCH_2CH_2OMe$, or a group selected from

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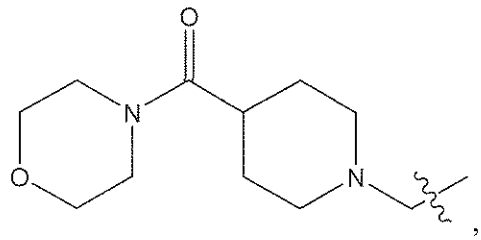
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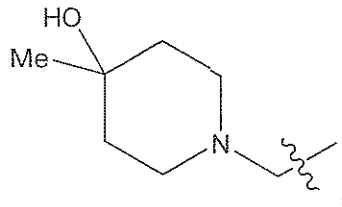
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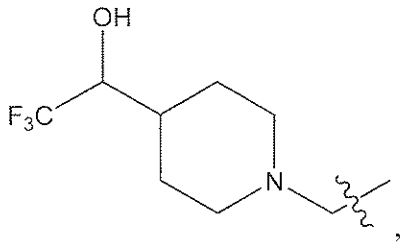
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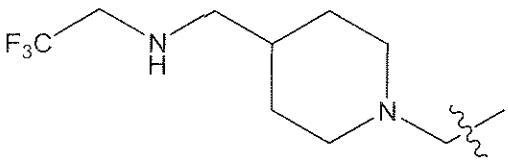
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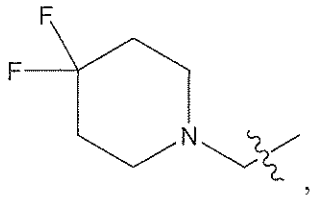
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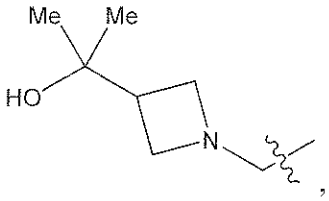
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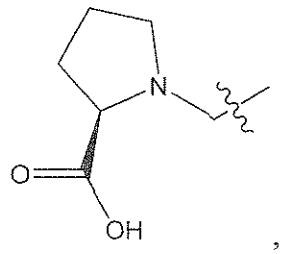
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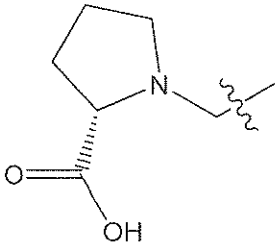
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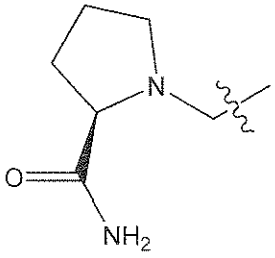
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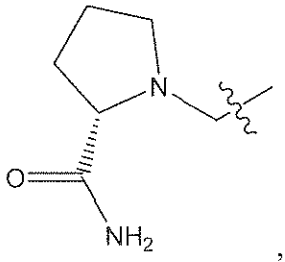
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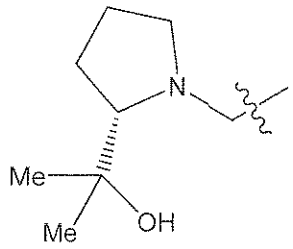
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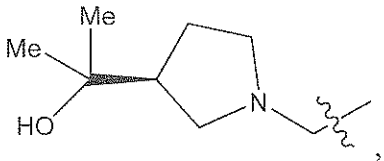
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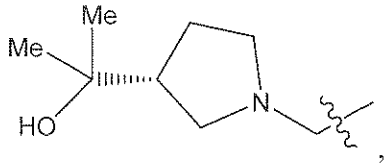
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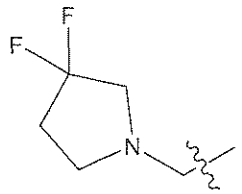
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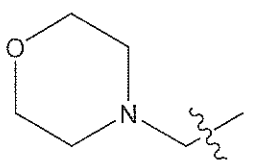
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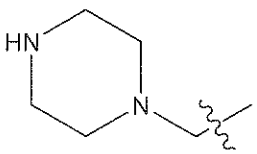
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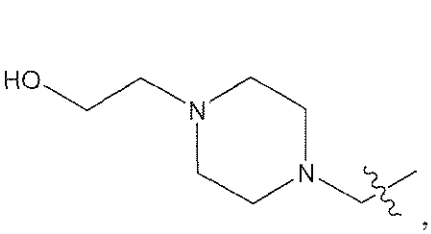
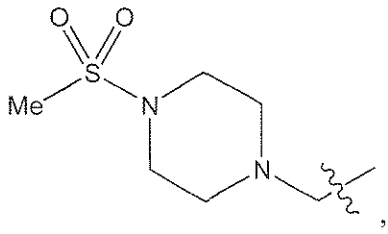
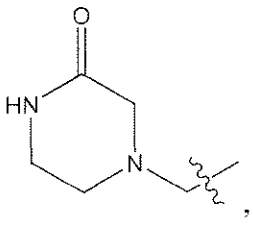
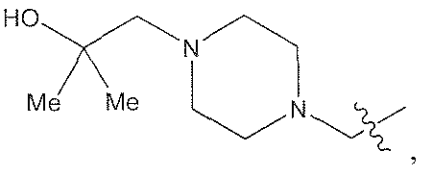
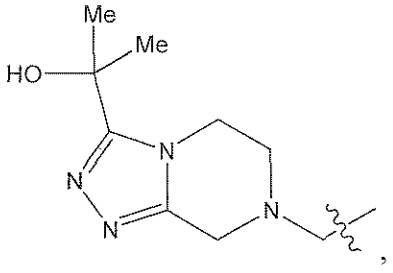
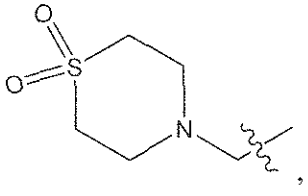
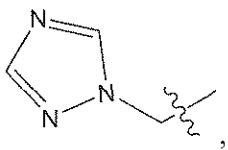
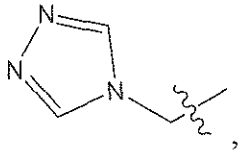
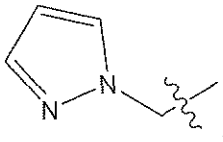
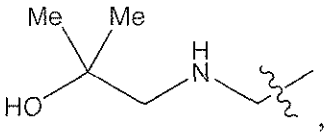
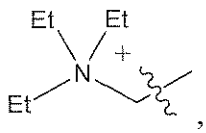
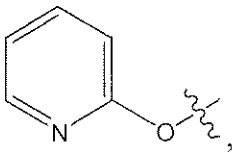
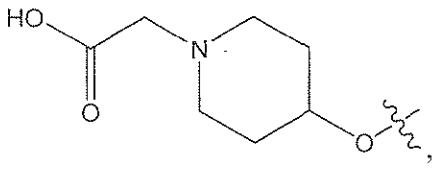
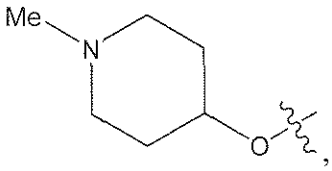
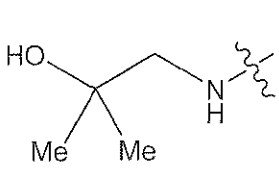
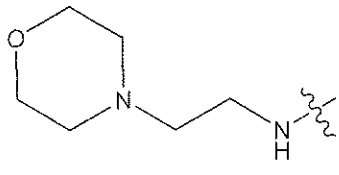
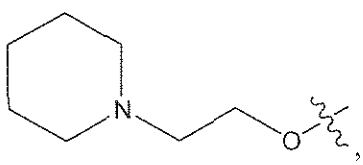
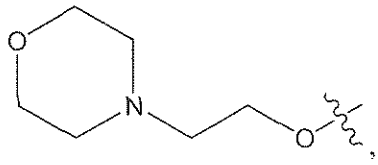
 ,  ,  ,

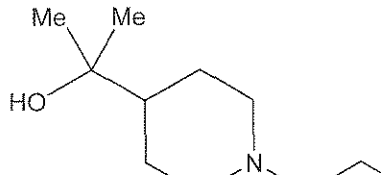
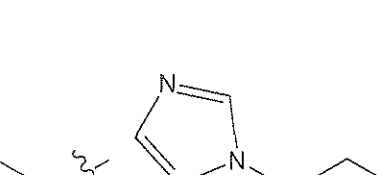
 ,  ,  ,

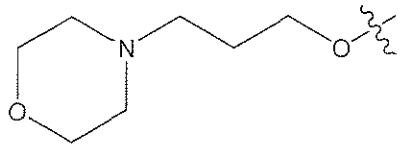
 ,  ,  ,  ,

 ,  ,  ,

 ,  ,  ,

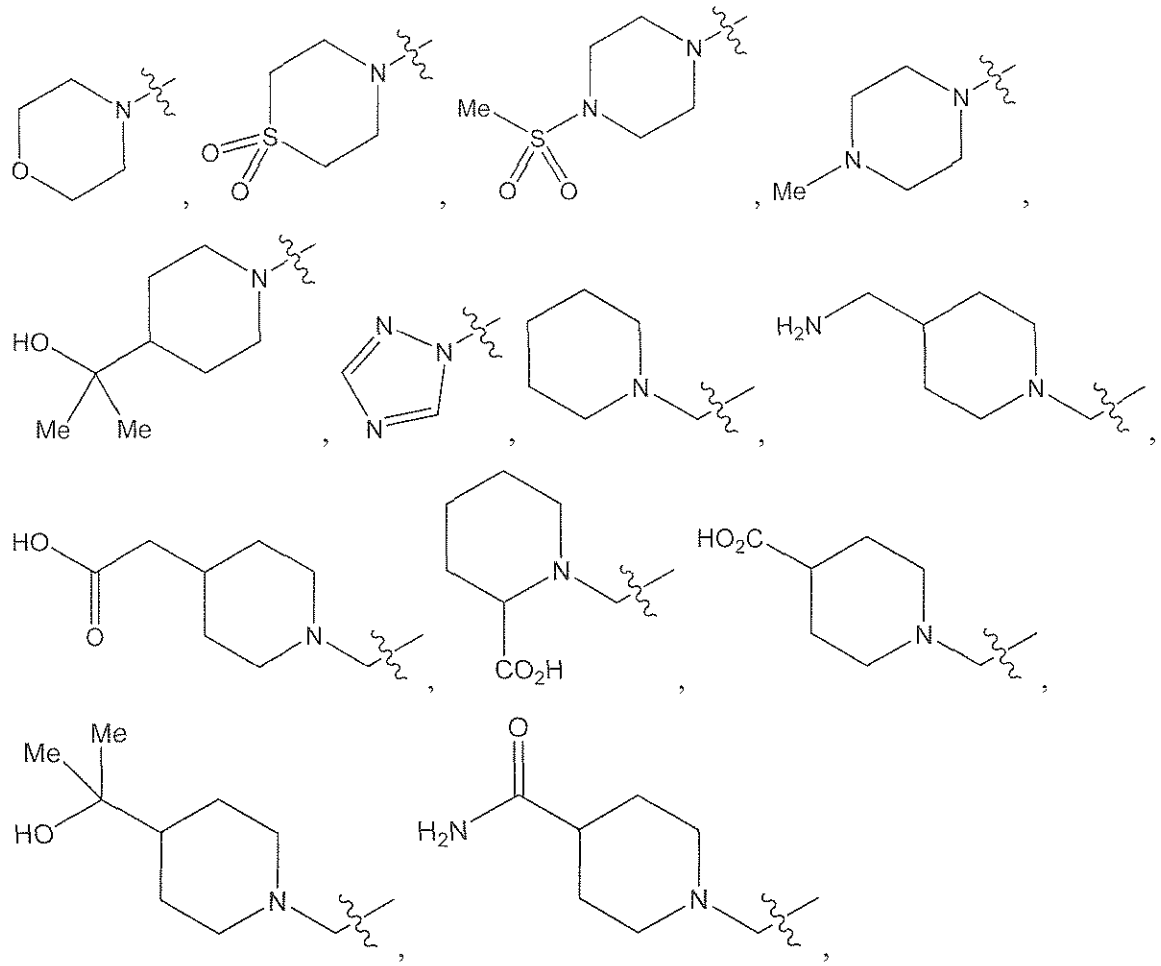
 ,  ,

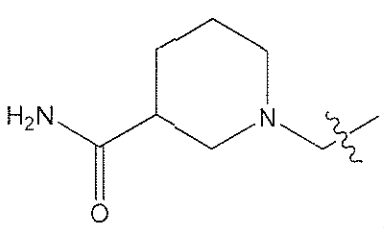
 ,  , or



, or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, or a stereoisomer of any of the foregoing, wherein the symbol ∿∿∿, when drawn across a bond, indicates the point of attachment to the rest of the molecule.

15. The compound of Claim 1, wherein W is selected from

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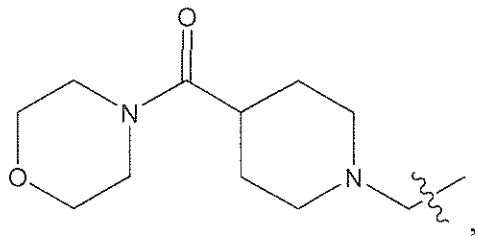
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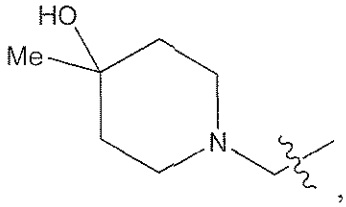
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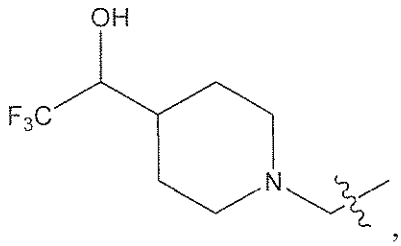
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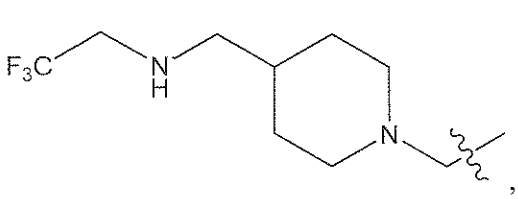
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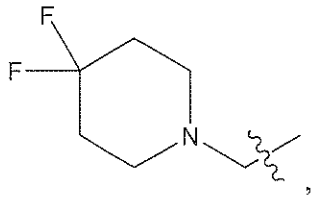
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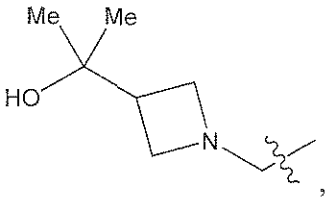
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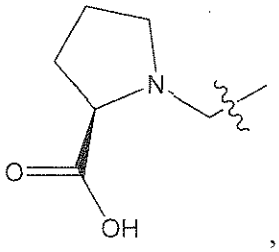
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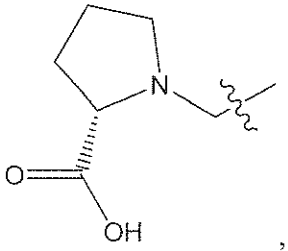
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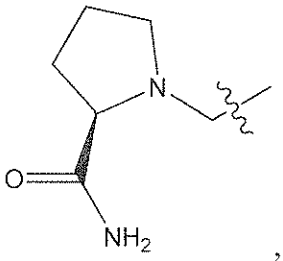
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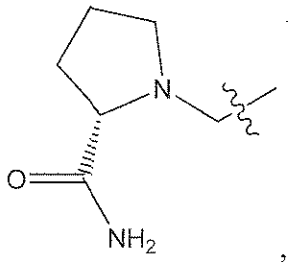
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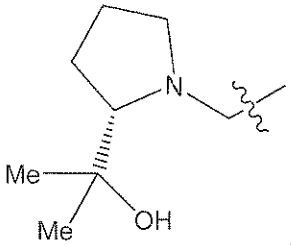
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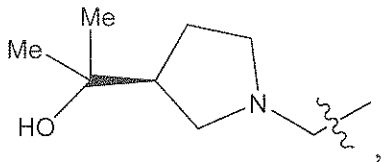
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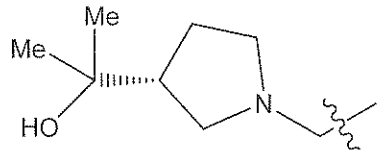
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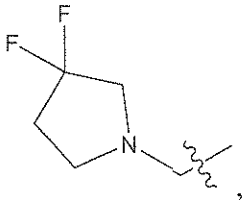
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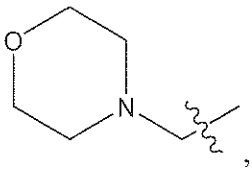
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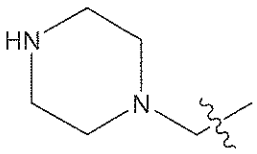
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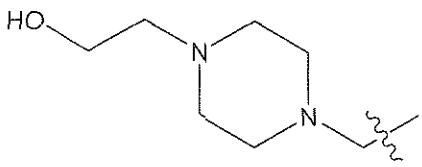
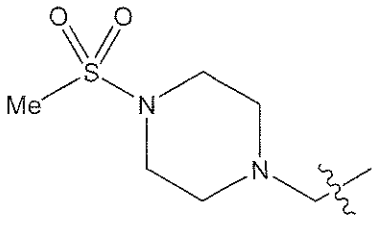
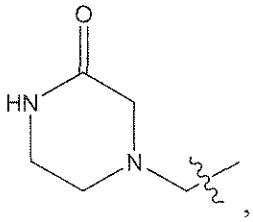
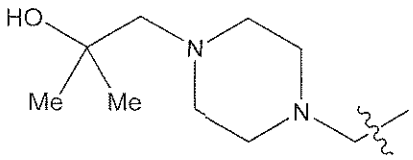
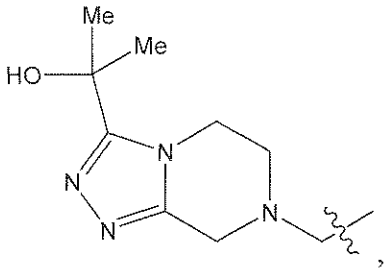
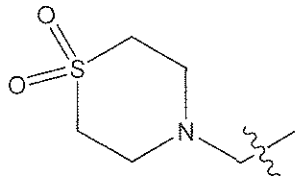
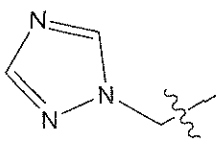
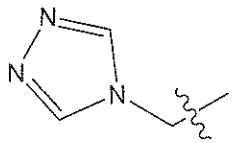
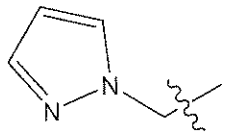
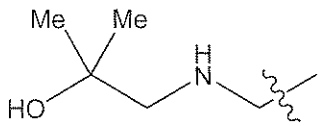
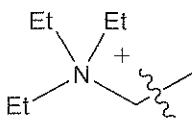
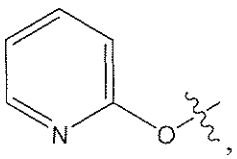
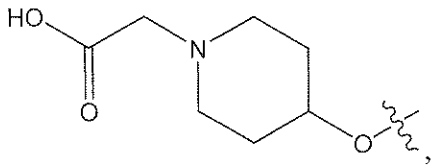
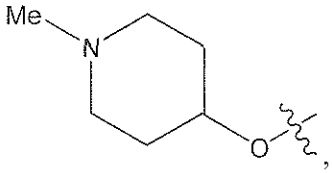
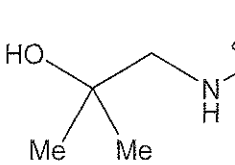
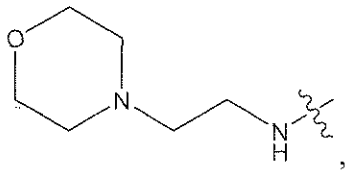
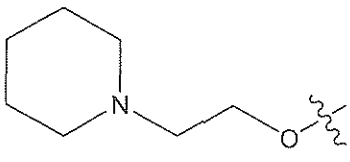
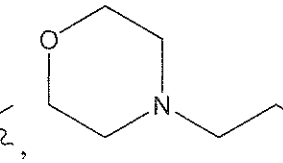
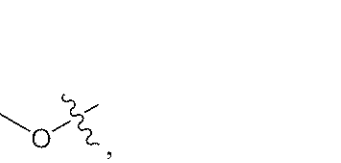
 ,  ,  ,

 ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,

 ,  ,  ,

 ,  ,  ,

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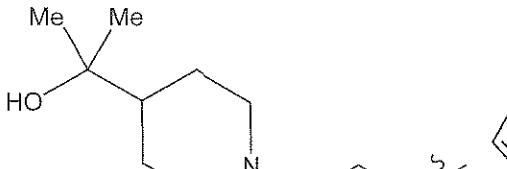
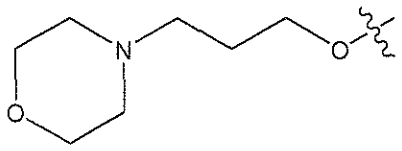
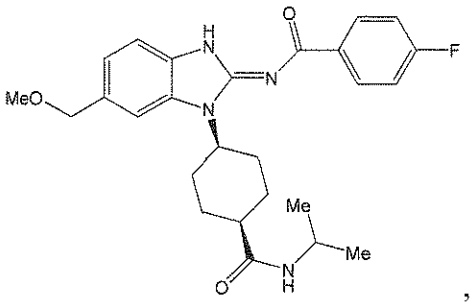
 ,  , or



, or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, or a stereoisomer of any of the foregoing, wherein the symbol ~~~, when drawn across a bond, indicates the point of attachment to the rest of the molecule.

16. The compound of Claim 1, wherein the compound is selected from,



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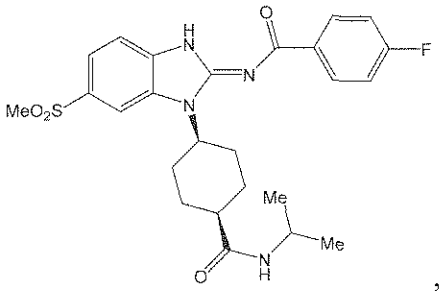
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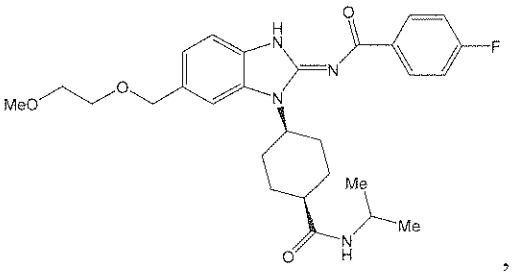
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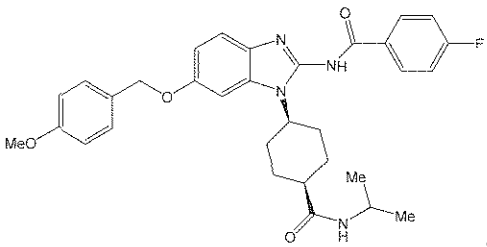
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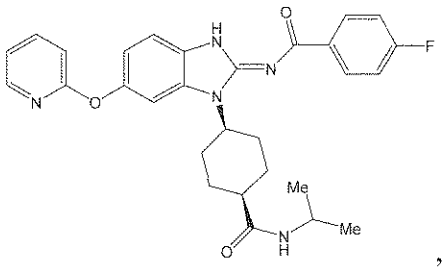
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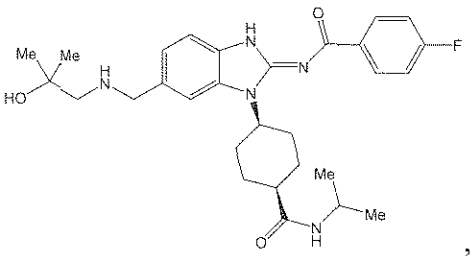
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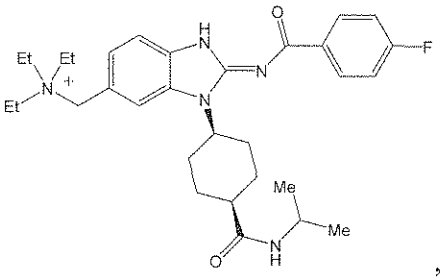
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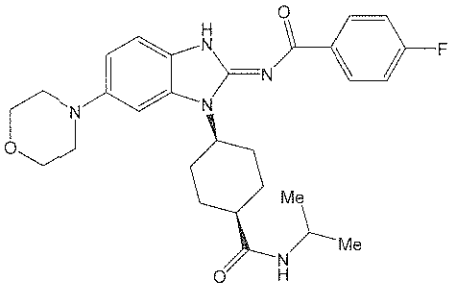
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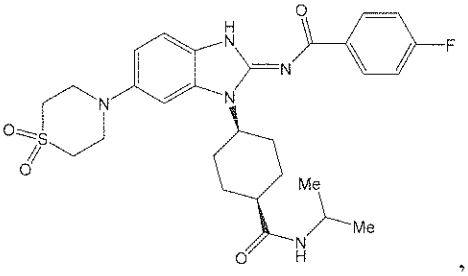
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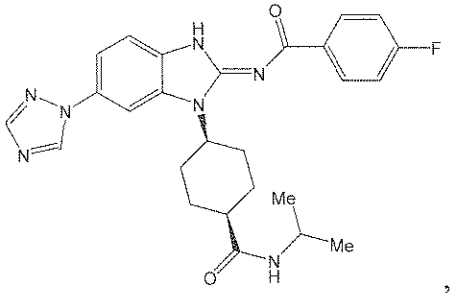
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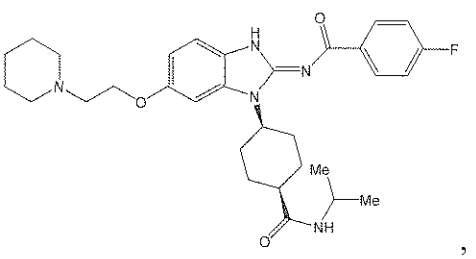
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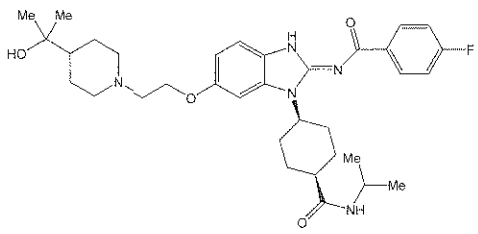
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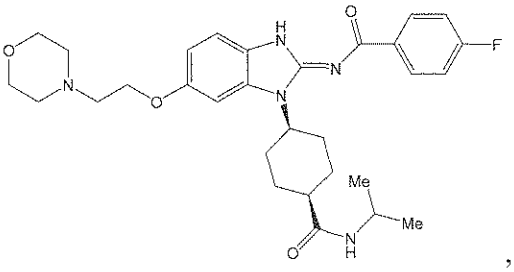
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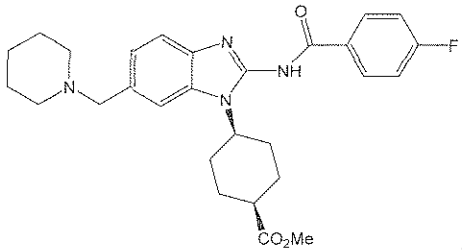
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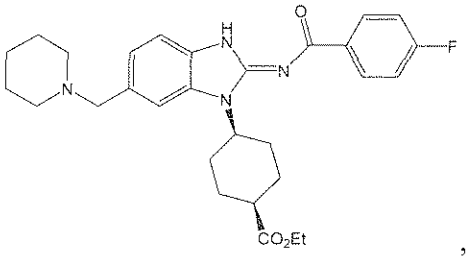
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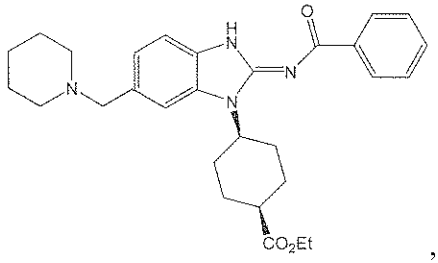
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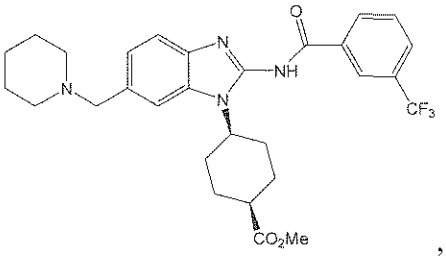
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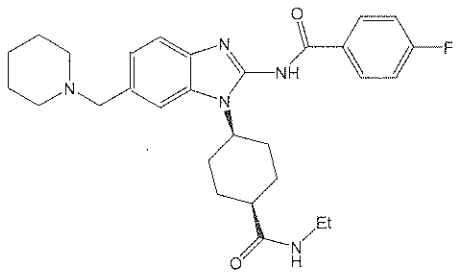
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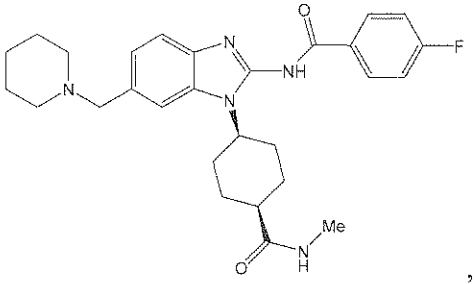
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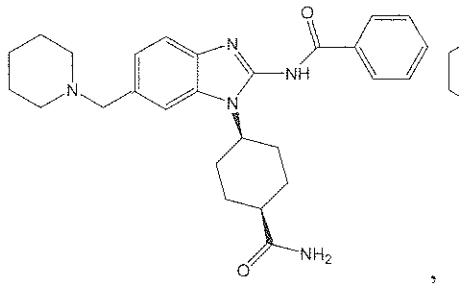
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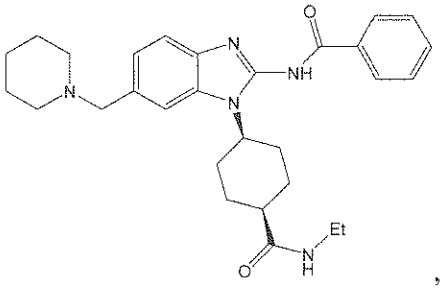
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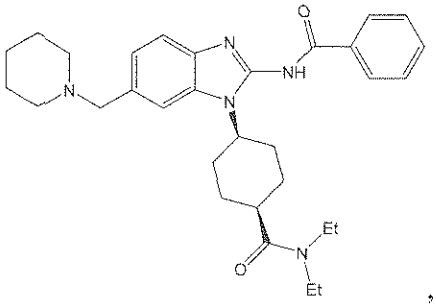
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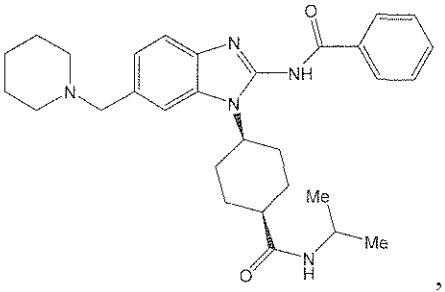
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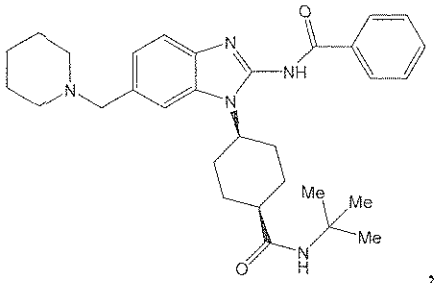
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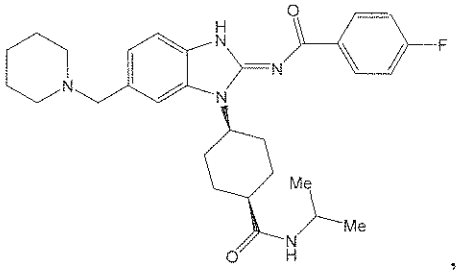
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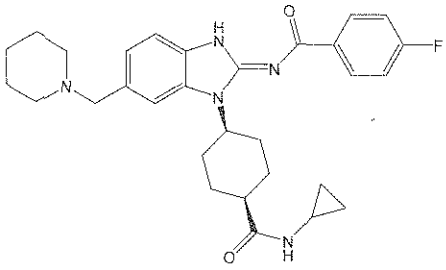
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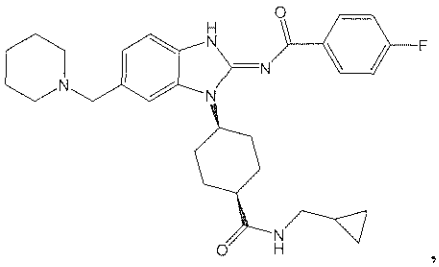
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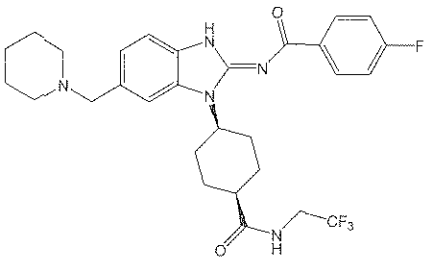
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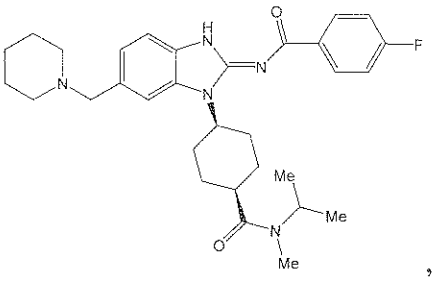
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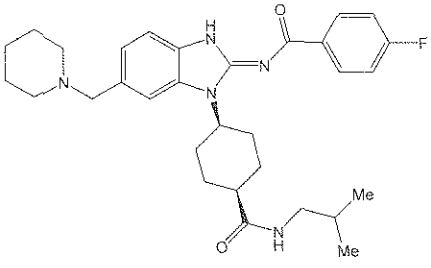
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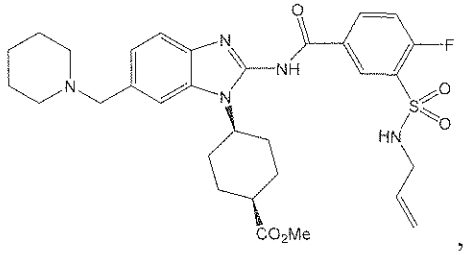
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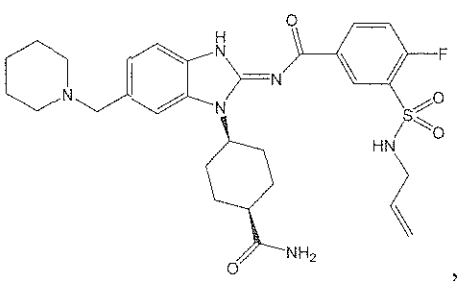
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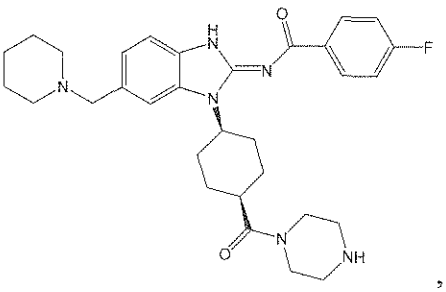
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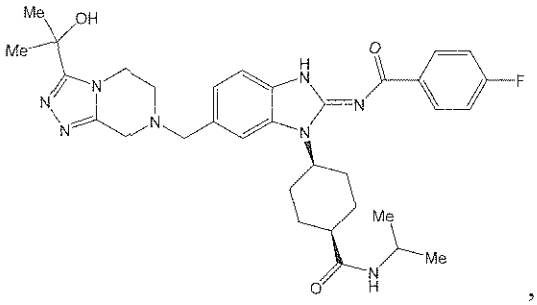
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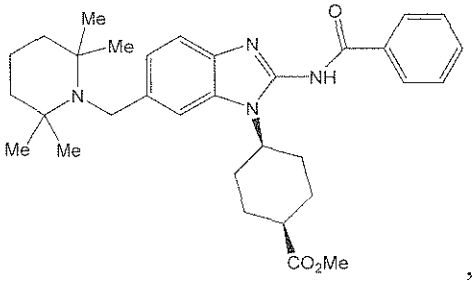
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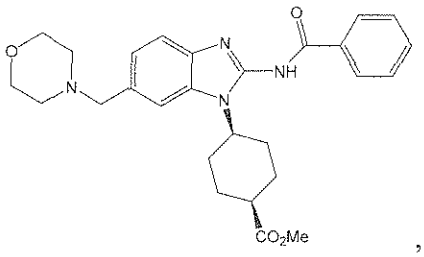
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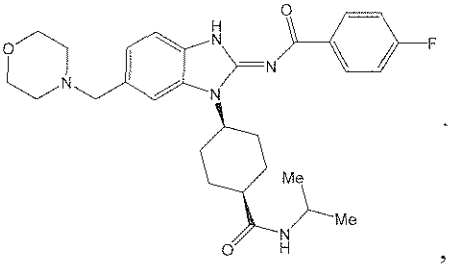
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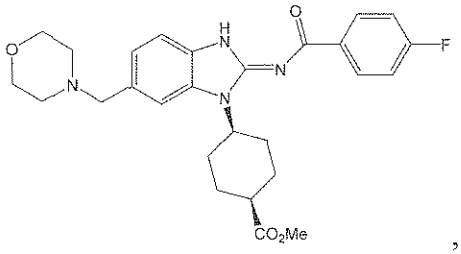
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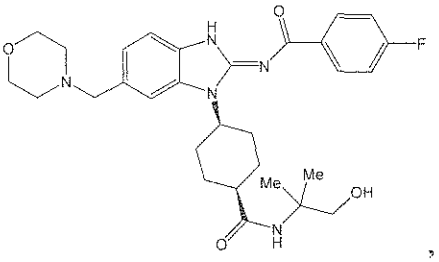
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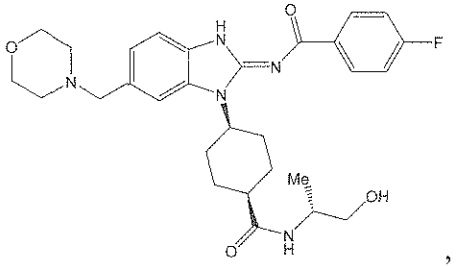
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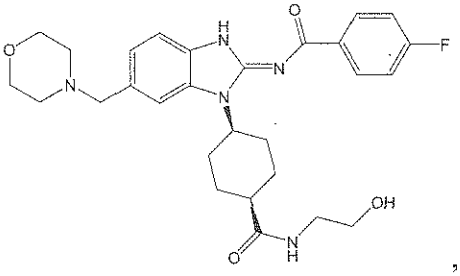
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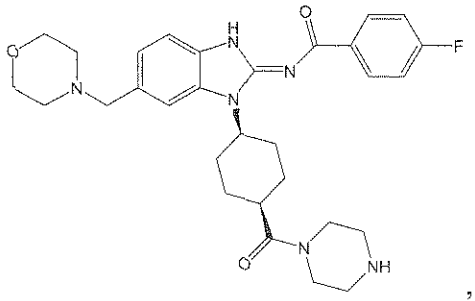
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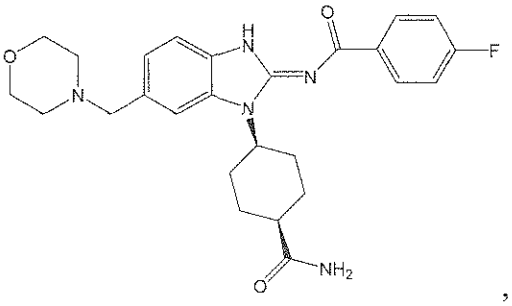
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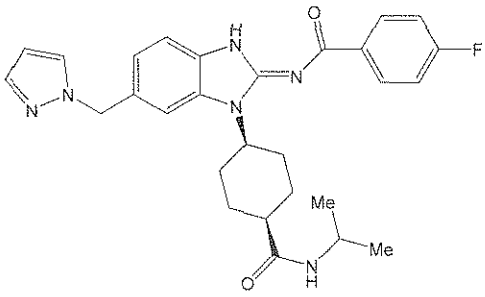
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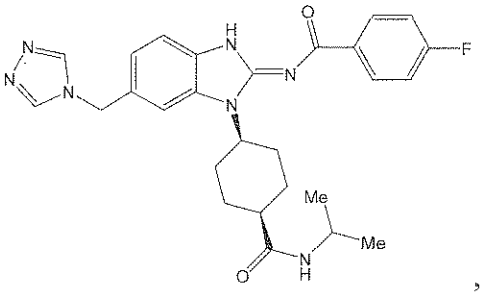
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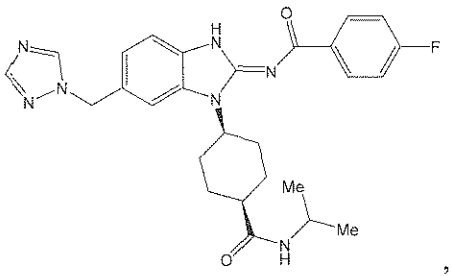
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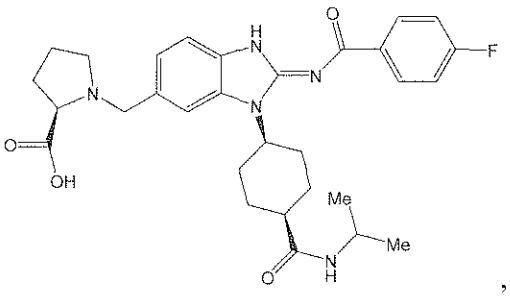
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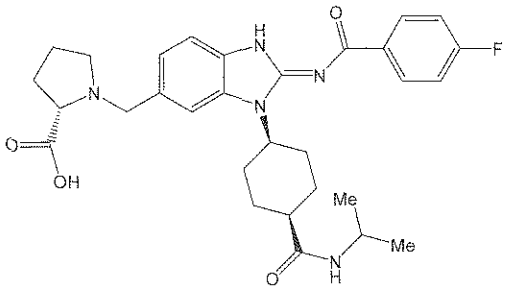
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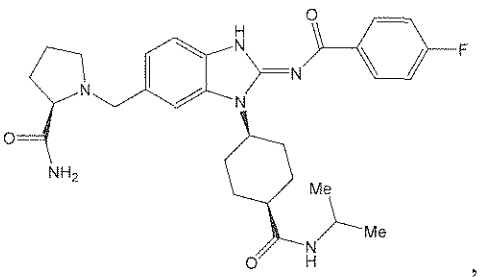
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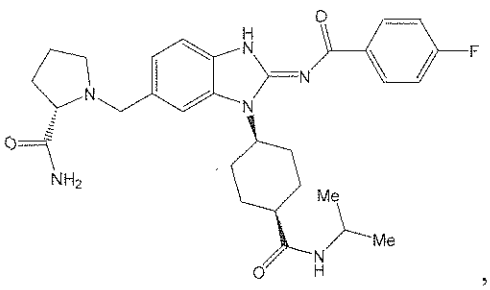
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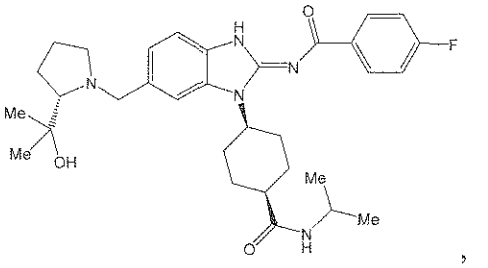
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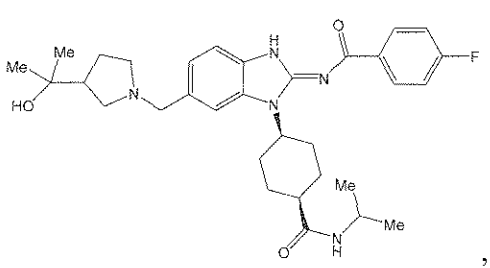
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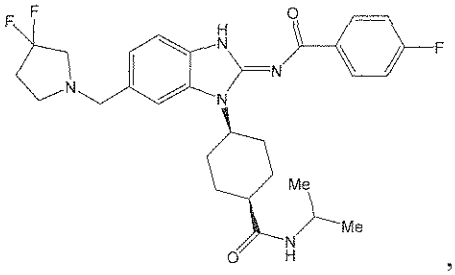
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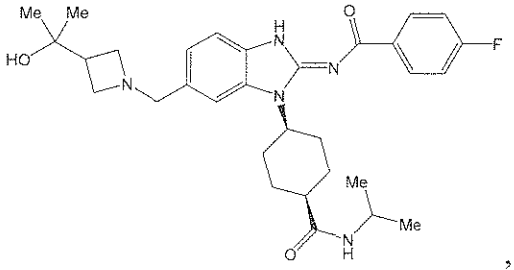
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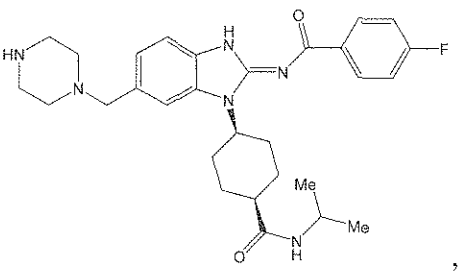
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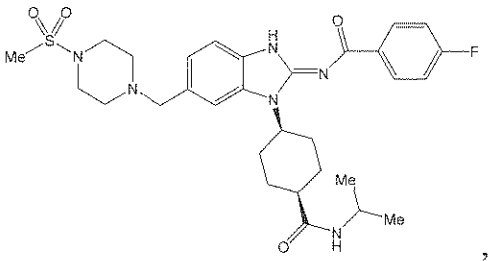
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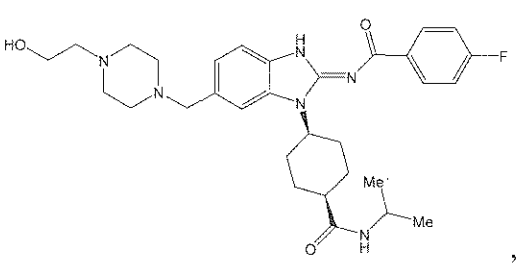
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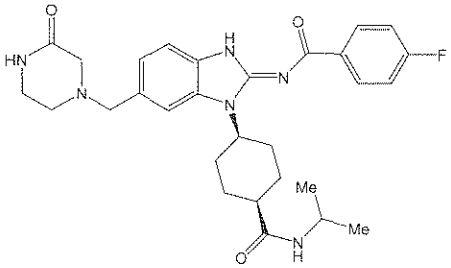
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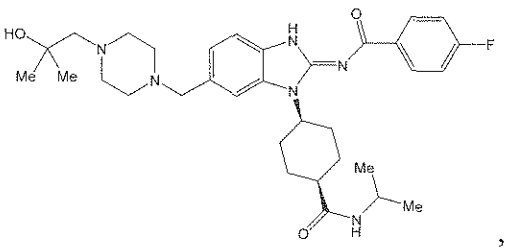
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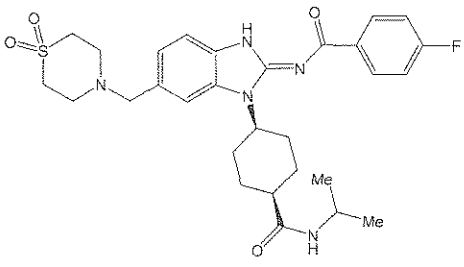
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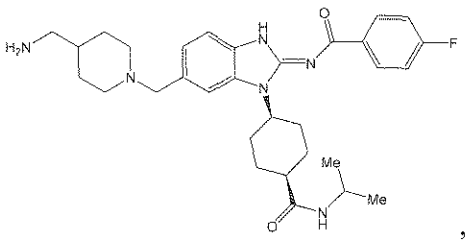
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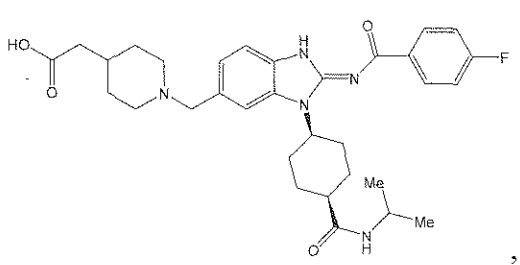
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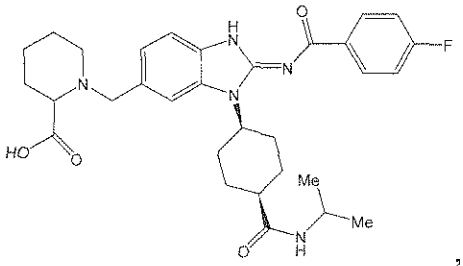
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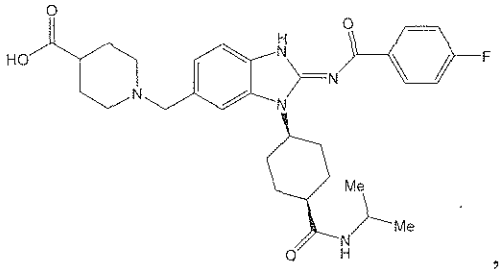
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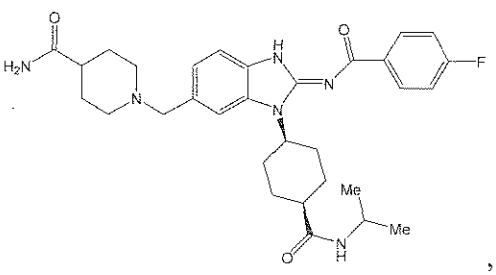
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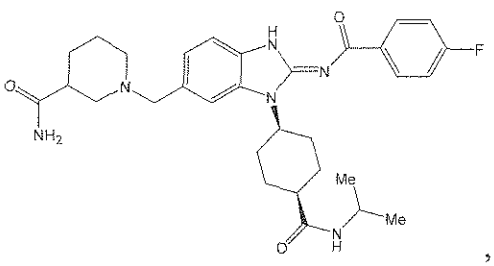
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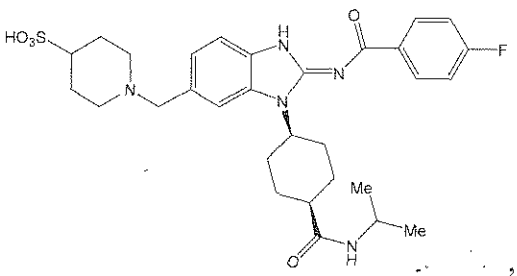
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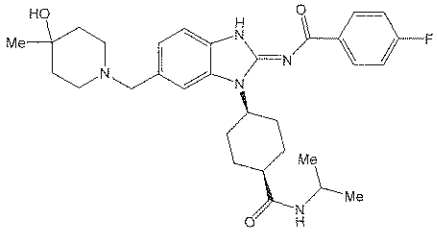
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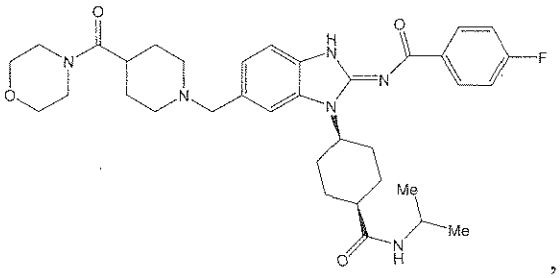
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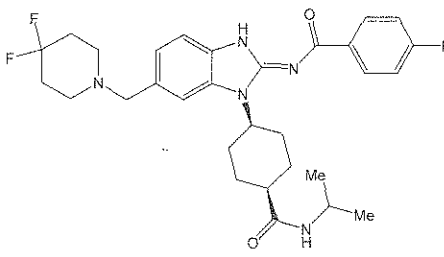
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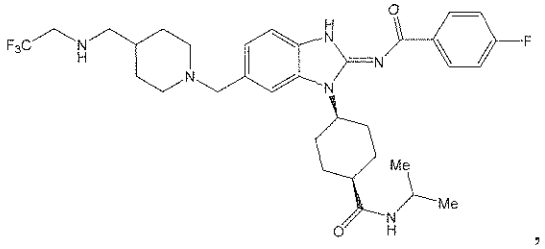
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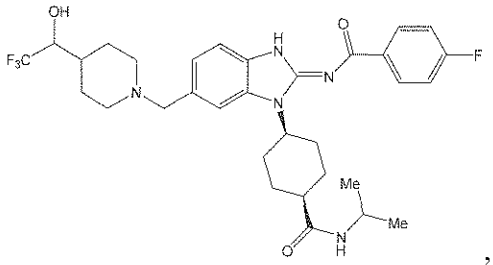
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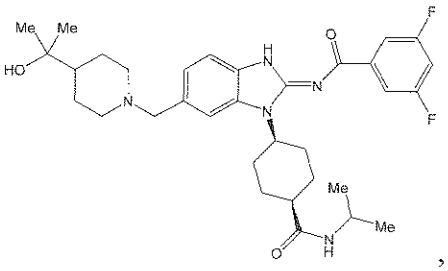
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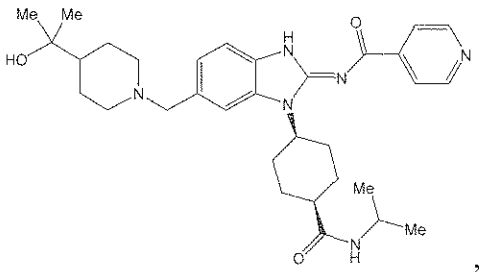
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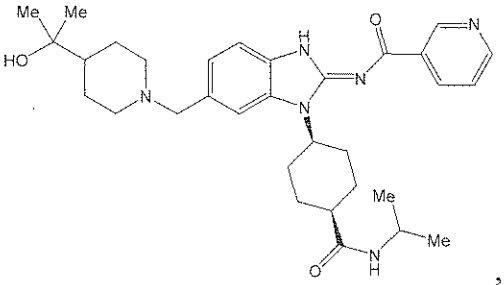
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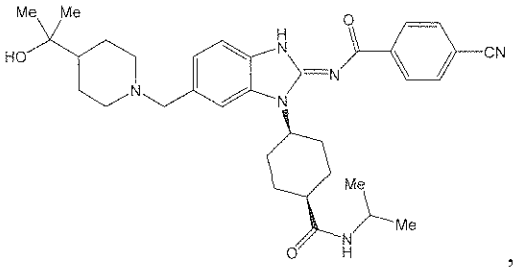
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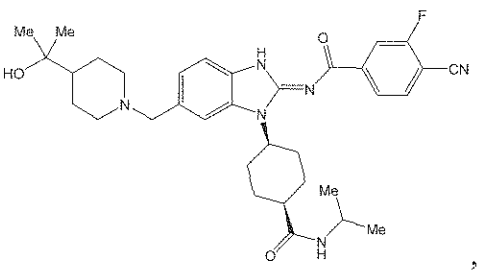
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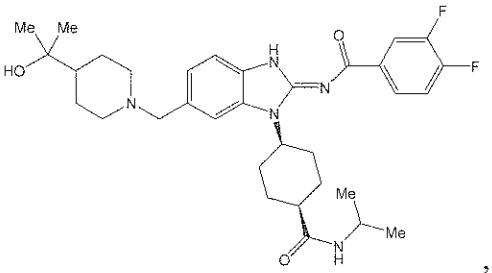
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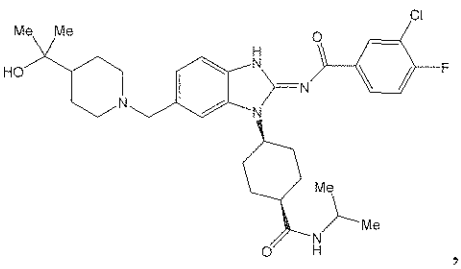
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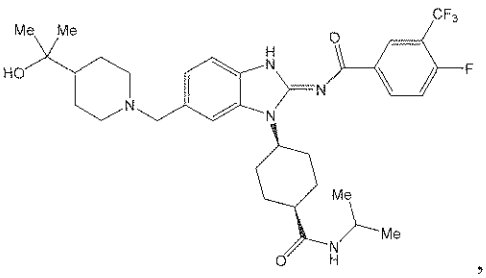
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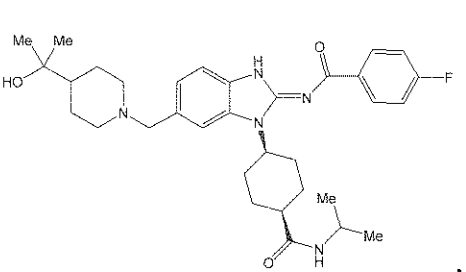
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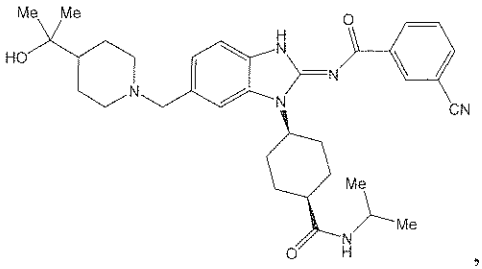
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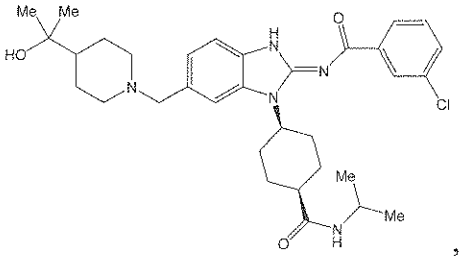
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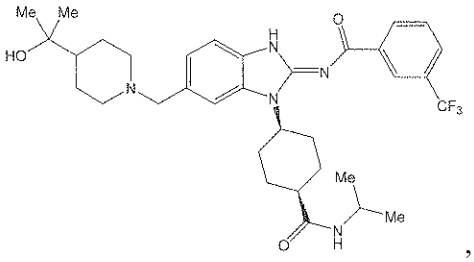
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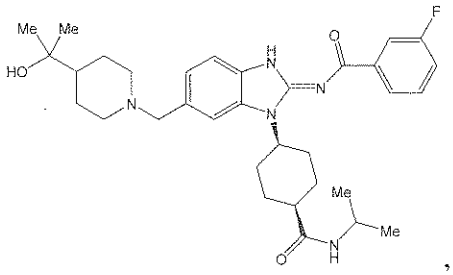
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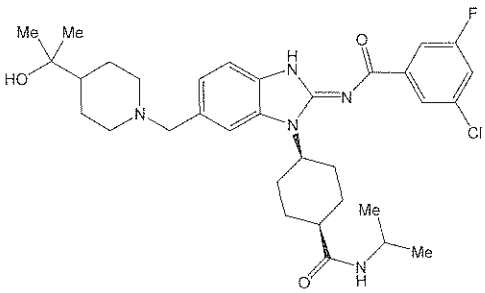
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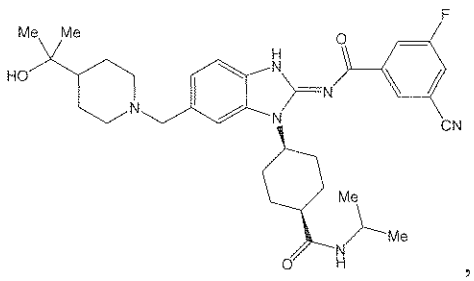
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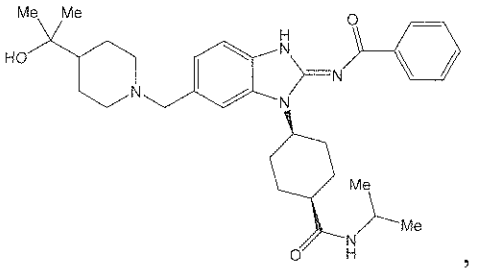
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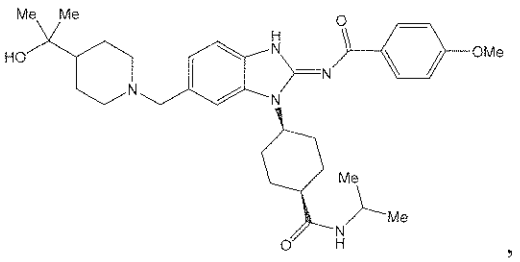
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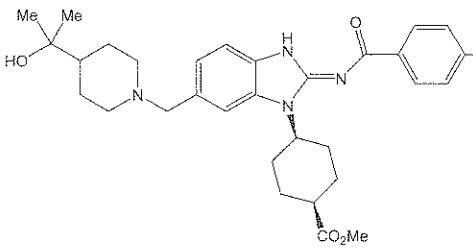
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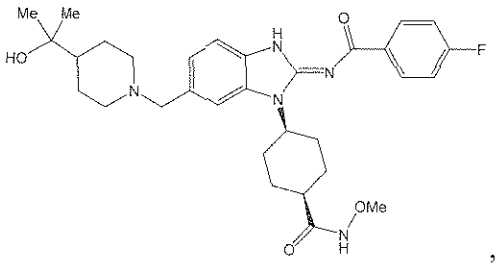
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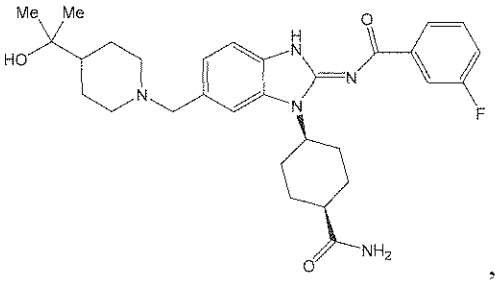
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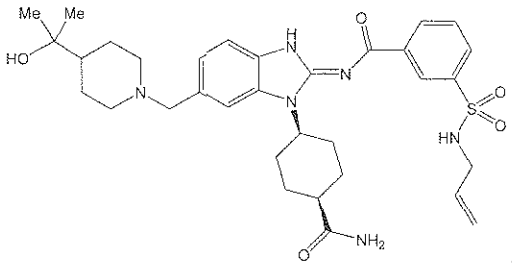
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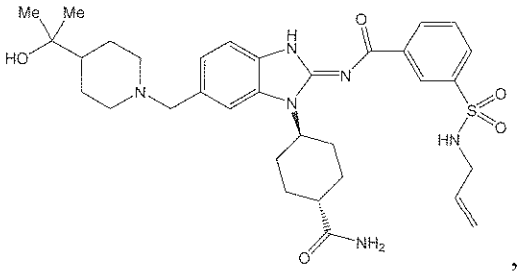
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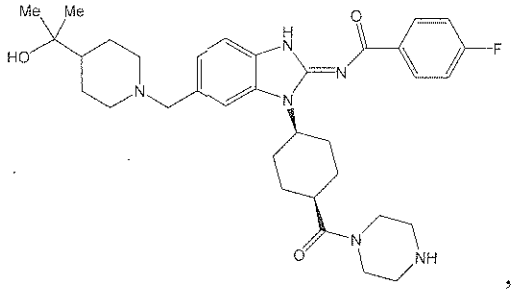
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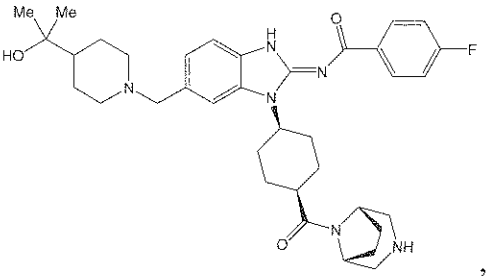
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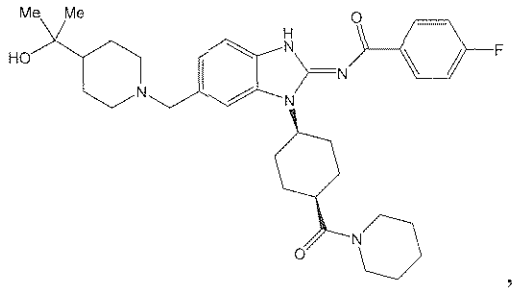
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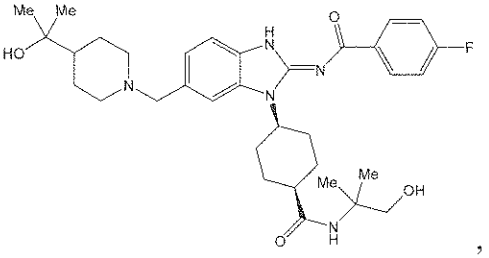
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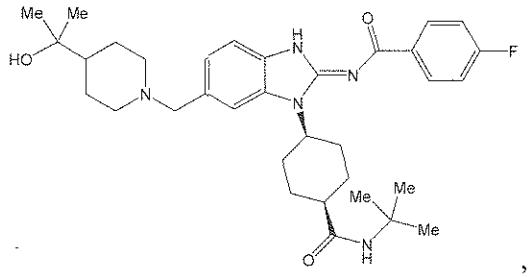
, or a pharmaceutically acceptable salt thereof, tautomer thereof, a pharmaceutically acceptable salt of the tautomer, or a stereoisomer of any of the foregoing.

17. A pharmaceutical composition comprising a therapeutically effective amount of the compound or the pharmaceutically acceptable salt thereof, tautomer thereof, the pharmaceutically acceptable salt of the tautomer, or the stereoisomer of any of the foregoing, according to Claim 1 and at least one pharmaceutically acceptable excipient, carrier, or diluent.