BICYCLIC AND TRICYCLIC DERIVATIVES AS THROMBIN RECEPTOR ANTAGONISTS

BACKGROUND OF THE INVENTION

The present invention relates to nor-seco himbacine derivatives, which can be useful as thrombin receptor antagonists in the treatment of diseases associated with thrombosis, atherosclerosis, restenosis, hypertension, angina pectoris, arrhythmia, heart failure, cerebral ischemia, stroke, neurodegenerative diseases and cancer. Thrombin receptor antagonists are also known as protease activated receptor-1 (PAR-1) antagonists. The compounds of the invention also can be useful as cannabinoid (CB_2) receptor inhibitors for the treatment of rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, diabetes, osteoporosis, renal ischemia, cerebral stroke, cerebral ischemia, nephritis, inflammatory disorders of the lungs and gastrointestinal tract, and respiratory tract disorders such as reversible airway obstruction, chronic asthma and bronchitis. The invention also relates to pharmaceutical compositions comprising said compounds.

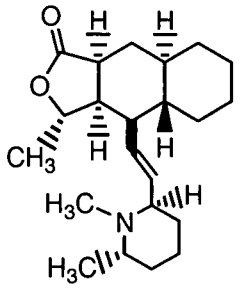
Thrombin is known to have a variety of activities in different cell types. Thrombin receptors are known to be present in such cell types as human platelets, vascular smooth muscle cells, endothelial cells and fibroblasts. It is therefore expected that thrombin receptor antagonists will be useful in the treatment of thrombotic, inflammatory, atherosclerotic and fibroproliferative disorders, as well as other disorders in which thrombin and its receptor play a pathological role.

Thrombin receptor antagonist peptides have been identified based on structure-activity studies involving substitutions of amino acids on thrombin receptors. In Bernatowicz *et al.*, J. Med. Chem., 39 (1996), p. 4879-4887, tetra- and pentapeptides are disclosed as being potent thrombin receptor antagonists, for example N-trans-cinnamoyl-p-fluoroPhe-p-guanidinoPhe-Leu-Arg-NH_2 and N-trans-cinnamoyl-p-fluoroPhe-p-guanidinoPhe-Leu-Arg-Arg-NH_2. Peptide thrombin receptor antagonists are also disclosed in WO 94/03479, published February 17, 1994.

Cannabinoid receptors belong to the superfamily of G-protein coupled receptors. They are classified into the predominantly neuronal CB_1 receptors and the predominantly peripheral CB_2 receptors. These receptors exert their biological actions by modulating adenylate cyclase and Ca^{+2} and K^+ currents. While the effects of CB_1

receptors are principally associated with the central nervous system, CB_2 receptors are believed to have peripheral effects related to bronchial constriction, immunomodulation and inflammation. As such, a selective CB_2 receptor binding agent is expected to have therapeutic utility in the control of diseases associated with rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, diabetes, osteoporosis, renal ischemia, cerebral stroke, cerebral ischemia, nephritis, inflammatory disorders of the lungs and gastrointestinal tract, and respiratory tract disorders such as reversible airway obstruction, chronic asthma and bronchitis (R. G. Pertwee, Curr. Med. Chem. *6*(8), (1999), 635; M. Bensaid, Molecular Pharmacology, 63 (4), (2003), 908.).

Himbacine, a piperidine alkaloid of the formula

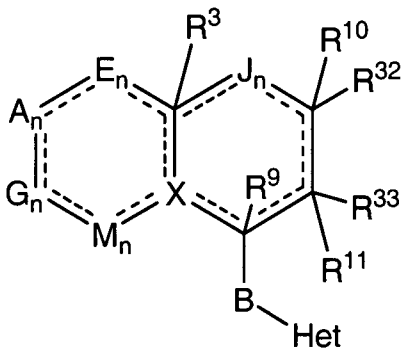


has been identified as a muscarinic receptor antagonist. The total synthesis of (+)-himbacine is disclosed in Chackalamannil *et al.*, J. Am. Chem. Soc., 118 (1996), p. 9812-9813.

Substituted tricyclic thrombin receptor antagonists are disclosed in US 6,063,847, US 6,326,380 and U.S. Serial Nos. 09/880222 (WO 01/96330) and 10/271715.

SUMMARY OF THE INVENTION

The present invention relates to compounds represented by the formula I:



formula I

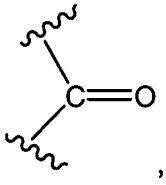
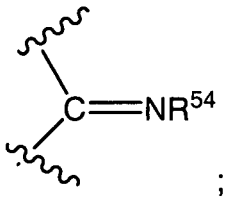
or a pharmaceutically acceptable salt, solvate, ester or prodrug of said compound, wherein

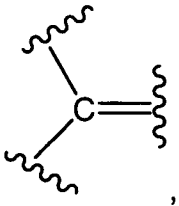
====== represents a double bond or a single bond, as permitted by the valency requirement; with the proviso that R^3 is absent when the carbon to which R^3 would be attached is part of a double bond;

B is $-(CH_2)_{n3}-$, $-(CH_2)-O-$, $-(CH_2)S-$, $-(CH_2)-NR^6-$, $-C(O)NR^6-$. $-NR^6C(O)-$,

 , $-(CH_2)_{n4}CR^{12}=CR^{12a}(CH_2)_{n5}-$ or $-(CH_2)_{n4}C\equiv C(CH_2)_{n5}-$, wherein n_3 is 0-5, n_4 and n_5 are independently 0-2, and R^{12} and R^{12a} are independently selected from the group consisting of hydrogen, alkyl and halogen;

A, E, G, M and J are independently selected from the group consisting of

$-N(R^{54})-$, $-(CR^1R^2)-$, $-O-$,  , $-S-$, $-S(O)-$, $-S(O)_2-$ and  ;

X is  , -CH- or –N-, with the proviso that selection of A, G, M and X do not result in adjacent oxygen or sulfur atoms;

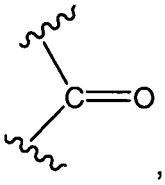
each n is 0, 1 or 2 with the proviso that all n variables cannot be 0;

Het is a mono-, bi- or tricyclic heteroaromatic group of 5 to 14 atoms comprised of 1 to 13 carbon atoms and 1 to 4 heteroatoms independently selected from the group consisting of N, O and S, with the proviso that there are no adjacent oxygen or sulfur atoms present in the heteroaromatic group, wherein a ring nitrogen can form an N-oxide or a quaternary group with an alkyl group, wherein Het is attached to B by a carbon atom ring member of Het, and wherein the Het group is substituted by 1 to 4 moieties, W, wherein each W is independently selected from the group consisting of hydrogen; alkyl; fluoroalkyl; difluoroalkyl; trifluoroalkyl; cycloalkyl; heterocycloalkyl; heterocycloalkyl substituted by alkyl or alkenyl; alkenyl; R^{21}-aryl; R^{21}-heteroaryl; R^{21}-arylalkyl; R^{21}-aryl-alkenyl; heteroaryl; heteroarylalkyl; heteroarylalkenyl; hydroxyalkyl; dihydroxyalkyl; aminoalkyl; alkylaminoalkyl;

di-(alkyl)-aminoalkyl; thioalkyl; alkoxy; alkenyloxy; halogen; $-NR^4R^5$; -CN; -OH;

-C(O)OR^{17}; -COR^{16}; -OS(O$_2$)CF$_3$; -CH$_2$OCH$_2$CF$_3$; alkylthio; -C(O)NR^{4}R^5; -OCHR^6-phenyl; phenoxyalkyl; -NHCOR^{16}; -NHSO$_2$R^{16}; biphenyl; -OC(R^6)$_2$COOR^7; -OC(R^6)$_2$C(O)NR^{4}R^5; alkoxy substituted by alkyl, amino or -NHC(O)OR^{17}; aryl;or alkyl optionally substituted with -NR^{1}R^2, -NR^{1}COR^2, -NR^{1}CONR^{1}R^2, -NR^{1}C(O)OR^2, -NR^{1}S(O)$_2$R^2, -NR^{1}S(O)$_2$NR^{1}R^2, -C(O)OH, -C(O)OR^1, -CONR^{1}R^2, hydroxyalkyl, alkyl or -S(O)$_2$-alkyl;-C(O)NR^{4}R^5 and heteroaryl; wherein adjacent carbons on the Het ring can optionally form a ring with a methylenedioxy group;

R^1 and R^2 are independently selected from the group consisting of hydrogen, alkyl, fluoroalkyl, difluoroalkyl, trifluoroalkyl, cycloalkyl, alkenyl, alkoxy, arylalkyl, arylalkenyl, heteroarylalkyl, heteroarylalkenyl, hydroxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, aryl and thioalkyl; or

R^1 and R^2 when attached to nitrogen, taken together, form a mono or bicyclic heterocyclic ring of 4 to 10 atoms, with 1-3 heteroatoms selected from –O-, -N-, -S-, -S(O)-, -S(O)$_2$- and  , with the proviso that S and O ring atoms are not adjacent to each other, where said heterocyclic ring is unsubstituted or substituted with one or more groups selected from alkyl, halogen, hydroxy, alkoxy, aryloxy and arylalkoxy;

R^3 is aralkoxy, aryloxy, heteroaryl, heteroaralkoxy, -CN, -NO$_2$, -O-aryl, -O-heteroaryl, N$_3$, –C(O)NR^{18}R^{19}, -C(=NR^1)NR^{1}R^2, -N(R^1)C=(NR^1)NR^{1}R^2; -N=C(R^1)NR^{1}R^2, -NR^{18}C(O)R^{19}, -NR^{18}C(O)NR^{18}R^{19}, -NR^{18}C(O)OR^{19}, -NR^{18}S(O)$_2$R^{19}, -NR^{18}S(O)$_2$NR^{18}R^{19}, -NHNR^{18}R^{19}, -NR^{18}NR^{18}R^{19} or -alkyl-NR^{18}R^{19};

R^6 is hydrogen, alkyl or phenyl;

R^7 is hydrogen or alkyl;

each R^{13} is independently selected from hydrogen, alkyl, cycloalkyl, haloalkyl, halogen, –(CH$_2$)$_{n6}$NHC(O)OR^{16b}, –(CH$_2$)$_{n6}$NHC(O)R^{16b}, –(CH$_2$)$_{n6}$NHC(O)NR^{4}R^5, –(CH$_2$)$_{n6}$NHSO$_2$R^{16}, –(CH$_2$)$_{n6}$NHSO$_2$NR^{4}R^5, and -(CH$_2$)$_{n6}$C(O)NR^{28}R^{29}, where n$_6$ is 0-4;

each R^{14} is independently selected from the group consisting of hydrogen, alkyl, -OH, alkoxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, halogen, haloalkyl, –(CH$_2$)$_{n6}$NHC(O)OR^{16b}, –(CH$_2$)$_{n6}$NHC(O)R^{16b}, –(CH$_2$)$_{n6}$NHC(O)NR^{4}R^5, –(CH$_2$)$_{n6}$NHSO$_2$R^{16}, –(CH$_2$)$_{n6}$NHSO$_2$NR^{4}R^5, and

$-(CH_2)_{n6}C(O)NR^{28}R^{29}$ where n_6 is 0-4; where R^4 and R^5 are independently selected from the group consisting of hydrogen, alkyl, phenyl, benzyl and cycloalkyl, or R^4 and R^5 together can form a ring with the nitrogen to which they are attached, wherein said ring formed by R^4 and R^5 is optionally substituted with =O, OH, OR^1 or –C(O)OH; or

R^{13} and R^{14} taken together form a spirocyclic or a heterospirocyclic ring of 3-6 ring atoms, wherein said heterospirocyclic ring contains 2 to 5 carbon ring atoms and 1 or 2 hetero ring atoms selected from the group consisting of O, S and N;

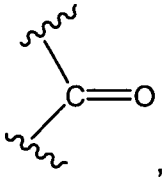
R^{16} is independently selected from the group consisting of hydrogen, alkyl, phenyl and benzyl;

R^{16a} is independently selected from the group consisting of hydrogen, alkyl, phenyl and benzyl;

R^{16b} is hydrogen, alkoxy, alkyl, alkoxyalkyl-, R^{22}-O-C(O)-alkyl-, cycloalkyl, R^{21}-aryl, R^{21}-arylalkyl, haloalkyl, alkenyl, halo substituted alkenyl, alkynyl, halo substituted alkynyl, R^{21}-heteroaryl, (R^{21}-heteroaryl)-alkyl-, (R^{21} –heterocycloalkyl)-alkyl-, $R^{28}R^{29}$N-alkyl-, $R^{28}R^{29}$N-C(O)-alkyl-, $R^{28}R^{29}$N-C(O)O-alkyl-, $R^{28}OC(O)N(R^{29})$-alkyl-, $R^{28}S(O)_2N(R^{29})$-alkyl-, $R^{28}R^{29}$N-C(O)-$N(R^{29})$-alkyl-, $R^{28}R^{29}$N-$S(O)_2N(R^{29})$-alkyl-, R^{28}-C(O)$N(R^{29})$-alkyl-, $R^{28}R^{29}$N-$S(O)_2$-alkyl-, $HOS(O)_2$-alkyl-, $(OH)_2P(O)_2$-alkyl-, R^{28}-S-alkyl-, R^{28}-$S(O)_2$-alkyl- or hydroxyalkyl;

R^{17} is independently selected from the group consisting of hydrogen, alkyl, phenyl and benzyl;

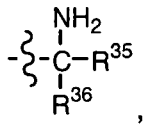
R^{18} and R^{19} are hydrogen, alkyl, aryl, R^{21}-aryl, heteroaryl, cycloalkyl, heterocyclyl, alkoxyalkyl, haloalkoxyalkyl, aryloxyalkyl, arylalkoxyalkyl, heteroaryloxyalkyl, heteroarylalkoxyalkyl, cycloalkyloxyalkyl, (heterocyclyl)alkyloxyalkyl, alkoxyalkyloxyalkyl, -$S(O)_2$-alkyl, –C(NH)NR^1R^2 or alkyl substituted with one or two moieties selected from cycloalkyl, halogen, hydroxy, -NR^1R^2, -NR^1C(O)R^2, -NR^1C(O)NR^1R^2, -NR^1C(O)OR^2, -$NR^1S(O)_2R^2$, -$NR^1S(O)_2NR^1R^2$, -C(O)OH, -C(O)OR^1 and -C(O)NR^1R^2; or

R^{18} and R^{19} together with the nitrogen to which they are attached, form a mono or bicyclic heterocyclic ring of 4 to 10 atoms, having 1-3 hetero ring atoms selected from –O-, -N-, -S-, -S(O)-, -$S(O)_2$- and  , with the proviso that S and O atoms

are not adjacent to each other, the ring being unsubstituted or substituted with one or more groups selected from alkyl, halogen, hydroxy, alkoxy, aryloxy, arylalkoxy, $-NR^1R^2$, $-NR^1COR^2$, $-NR^1C(O)NR^1R^2$, $-NR^1C(O)OR^2$, $-NR^1S(O)_2R^2$, $-NR^1S(O_2)NR^1R^2$, $-C(O)OR^1$, $-CONR^1R^2$ and alkyl substituted with $-NR^1R^2$, $-NR^1COR^2$, $-NR^1CONR^1R^2$, $-NR^1C(O)OR^2$, $-NR^1S(O)_2R^2$, $-NR^1S(O)_2NR^1R^2$, $-C(O)OR^1$ or $-CONR^1R^2$;

R^{21} is 1 to 3 moieties and each R^{21} is independently selected from the group consisting of hydrogen, -CN, $-CF_3$, $-OCF_3$, halogen, $-NO_2$, alkyl, -OH, alkoxy, alkylamino-, di-(alkyl)amino-, $-NR^{25}R^{26}$alkyl-, hydroxyalkyl-, $-C(O)OR^{17}$, $-COR^{17}$, $-NHCOR^{16}$, $-NHS(O)_2R^{16}$, $-C(NH)-NH_2$, $-NHS(O)_2CH_2CF_3$, $-C(O)NR^{25}R^{26}$, $-NR^{25}-C(O)-NR^{25}R^{26}$, $-S(O)R^{13}$, $-S(O)_2R^{13}$, $-SR^{13}$; $-SO_2NR^4R^5$ and $-CONR^4R^5$; or two adjacent R^{21} moieties can form a methylenedioxy group;

R^{22} is hydrogen, alkyl, phenyl, benzyl, $-COR^{16}$, $-CONR^{18}R^{19}$, $-COR^{23}$, $-S(O)R^{31}$, $-S(O)_2R^{31}$, $-S(O_2)NR^{24}R^{25}$ or $-C(O)OR^{27}$;

R^{23} is  , wherein R^{35} and R^{36} are independently selected from the group consisting of hydrogen, alkyl, and R^{37}-substituted alkyl, wherein R^{37} is selected from the group consisting of HO-, HS-, CH_2S-, $-NH_2$, phenyl, p-hydroxyphenyl and indolyl; or R^{23} is alkyl; haloalkyl; alkenyl; haloalkenyl; alkynyl; cycloalkyl; cycloalkylalkyl; cycloalkyl substituted by 1 to 3 substituents selected from the group consisting of alkoxyalkyl, alkyl, halogen, hydroxy, alkoxy, aryloxy, arylalkoxy, $-NR^1R^2$, $-NR^1C(O)R^2$, $-NR^1C(O)NR^1R^2$, $-NR^1C(O)OR^2$, $-NR^1S(O)_2R^2$, $-NR^1S(O)_2NR^1R^2$, -C(O)OH, $-C(O)OR^1$ and $-CONR^1R^2$; aryl; aralkyl; heteroaryl; heterocycloalkyl; alkyl substituted with $-NR^1R^2$, $-NR^1COR^2$, $-NR^1CONR^1R^2$, $-NR^1C(O)OR^2$, $-NR^1S(O_2)R^2$, $-NR^1S(O_2)NR^1R^2$, -C(O)OH, $-C(O)OR^1$, $-CONR^1R^2$ and $-SO_3H$;

R^{24}, R^{25} and R^{26} are independently selected from the group consisting of hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, halocycloalkyl, alkoxyalkyl, hydroxy and alkoxy;

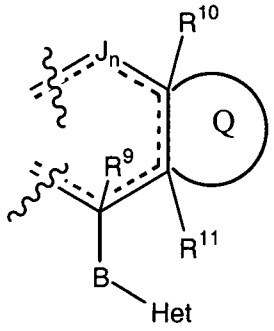
R^{27} is 1 to 3 moieties and each R^{27} is selected from the group consisting of hydrogen, alkyl, and cycloalkyl, wherein R^{27} is optionally substituted with -OH, -C(O)OH, halogen and alkoxy;

R^{28} and R^{29} are independently selected from the group consisting of hydrogen, alkyl, alkoxy, arylalkyl, heteroaryl, heteroarylalkyl, hydroxyalkyl, alkoxyalkyl, heterocyclyl, heterocyclylalkyl, and haloalkyl; or

R^{28} and R^{29} taken together form a spirocyclic or a heterospirocyclic ring having 3-6 ring atoms;

R^{32} and R^{33} are independently selected from the group consisting of hydrogen, R^{34}- alkyl, R^{34}-alkenyl, R^{34}-alkynyl, R^{40}-heterocycloalkyl, R^{38}-aryl, R^{38}-aralkyl, R^{42}-cycloalkyl, R^{42}-cycloalkenyl, -OH, $-OC(O)R^{43}$, $-C(O)OR^{43}$, $-C(O)R^{43}$, $-C(O)NR^{43}R^{44}$, $-NR^{43}R^{44}$, $-NR^{43}C(O)R^{44}$, $-NR^{43}C(O)NR^{44}R^{45}$, $-NHS(O)_2R^{43}$, $-OC(O)NR^{43}R^{44}$, R^{37}-alkoxy, R^{37}-alkenyloxy, R^{37}-alkynyloxy, R^{40}-heterocycloalkyloxy, R^{42}-cycloalkyloxy, R^{42}-cyclo-alkenyloxy, R^{42}-cycloalkyl-NH-, $-NHSO_2NHR^{16}$ and $-CH(=NOR^{17})$;

or R^{32} and R^{33} can be combined to form a ring structure Q, below

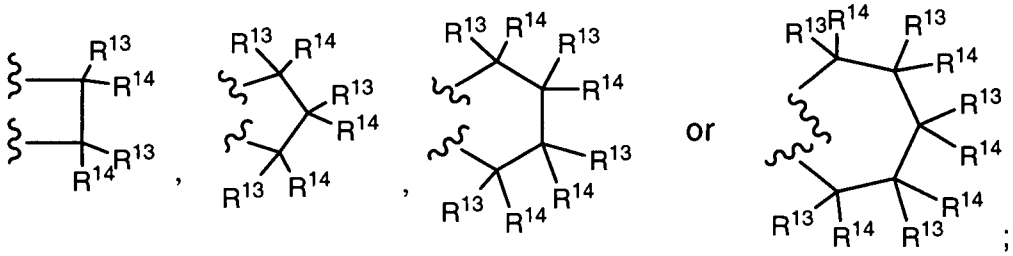


where

R^9 is hydrogen, OH, alkoxy, halogen or haloalkyl;

Q is fused R-substituted aryl, R-substituted heteroaryl, R-substituted heterocyclic ring of 4-8 atoms containing 1-3 heteroatoms selected from O, S, S(O), $S(O)_2$ and NR^{22} with the proviso that S and O cannot be adjacent to one another; or

Q is



;

wherein R^{10} and R^{11} are independently selected from the group consisting of R^1 and $-OR^1$, provided that when ring Q is aromatic and the carbon atoms bearing R^{10} and R^{11} are connected by a double bond, R^{10} and R^{11} are absent;

R is 1 to 5 moieties and each R is independently selected from the group consisting of hydrogen, alkyl, halogen, hydroxy, amino, alkylamino, dialkylamino, alkoxy, -COR^{16}, -$C(O)OR^{17}$, -$C(O)NR^4R^5$, -SOR^{16}, -$S(O_2)R^{16}$, -$NR^{16}COR^{16a}$, -$NR^{16}C(O)OR^{16a}$, -$NR^{16}CONR^4R^5$, -$NR^{16}S(O_2)NR^4R^5$, fluoroalkyl, difluoroalkyl, trifluoroalkyl, cycloalkyl, alkenyl, arylalkyl, arylalkenyl, heteroarylalkyl, heteroarylalkenyl, hydroxyalkyl, aminoalkyl, aryl and thioalkyl;

R^{34} is 1 to 3 moieties and each R^{34} is independently selected from the group consisting of hydrogen, halogen, -OH, alkoxy, R^{47}-aryl, alkyl-C(O)-, alkenyl-C(O)-, alkynyl-C(O)-, heterocycloalkyl, R^{39}-cycloalkyl, R^{39}-cycloalkenyl, -$OC(O)R^{43}$, -$C(O)OR^{43}$, -$C(O)R^{43}$, -$C(O)NR^{43}R^{44}$, -$NR^{43}R^{44}$, -$NR^{43}C(O)R^{44}$, -$NR^{43}C(O)NR^{44}R^{45}$, -$NHSO_2R^{43}$, -$OC(O)NR^{43}R^{44}$, R^{34}-alkenyloxy, R^{34}-alkynyloxy, R^{40}-heterocycloalkyloxy, R^{42}- cycloalkyloxy, R^{42}-cycloalkenyloxy, R^{42}-cycloalkyl-NH-, –$NHSO_2NHR^{16}$ and –$CH(=NOR^{17})$;

R^{38} is 1 to 3 moieties and each R^{38} is independently selected from the group consisting of hydrogen, heterocycloalkyl, halogen, -$C(O)OR^{48}$, -CN, -$C(O)NR^{49}R^{50}$, -$NR^{51}C(O)R^{52}$, -OR^{48}, cycloalkyl, cycloalkylalkyl, alkylcycloalkylalkyl, haloalkylcycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, and R^{52}-heteroaryl; or two R^{38} groups on adjacent ring carbons form a fused methylenedioxy group;

R^{39} is 1 to 3 moieties and each R^{39} is independently selected from the group consisting of hydrogen, halogen and alkoxy;

R^{40} is 1 to 3 moieties and each R^{40} is independently selected from the group consisting of hydrogen, R^{41}-alkyl, R^{41}-alkenyl and R^{41}-alkynyl;

R^{41} is hydrogen, -OH or alkoxy;

R^{42} is 1 to 3 moieties and each R^{42} is independently selected from the group consisting of hydrogen, alkyl, -OH, alkoxy and halogen;

R^{43}, R^{44} and R^{45} are independently selected from the group consisting of hydrogen, alkyl, alkoxyalkyl, R^{38}-arylalkyl, R^{46}-cycloalkyl, R^{53}-cycloalkylalkyl, R^{38}-aryl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl and heteroarylalkyl;

R^{46} is hydrogen, alkyl, hydroxyalkyl or alkoxy;

R^{47} is 1 to 3 moieties and each R^{47} is independently selected from the group consisting of hydrogen, alkyl, -OH, halogen, -CN, alkoxy, trihaloalkoxy, alkylamino, di(alkyl)amino, -OCF_3, hydroxyalkyl, -CHO, -C(O)alkylamino, -C(O)di(alkyl)amino, -NH_2, -NHC(O)alkyl and -N(alkyl)C(O)alkyl;

R^{48} is hydrogen, alkyl, haloalkyl, dihaloalkyl or trifluoroalkyl;

R^{49} and R^{50} are independently selected from the group consisting of hydrogen, alkyl, aralkyl, phenyl and cycloalkyl, or R^{49} and R^{50} together are $-(CH_2)_4-$, $-(CH_2)_5-$ or $-(CH_2)_2-NR^{39}-(CH_2)_2-$ and form a ring with the nitrogen to which they are attached;

R^{51} and R^{52} are independently selected from the group consisting of hydrogen, alkyl, aralkyl, phenyl and cycloalkyl, or R^{51} and R^{52} in the group $-NR^{39}C(O)R^{40}$, together with the nitrogen atoms to which they are attached, form a cyclic lactam having 5-8 ring members;

R^{53} is hydrogen, alkoxy, $-SOR^{16}$, $-SO_2R^{17}$, $-C(O)OR^{17}$, $-C(O)NR^{18}R^{19}$, alkyl, halogen, fluoroalkyl, difluoroalkyl, trifluoroalkyl, cycloalkyl, alkenyl, aralkyl, arylalkenyl, heteroarylalkyl, heteroarylalkenyl, hydroxyalkyl, aminoalkyl, aryl, thioalkyl, alkoxyalkyl or alkylaminoalkyl;

and

R^{54} is selected from the group consisting of hydrogen; alkyl; fluoroalkyl; difluoroalkyl; trifluoroalkyl; cycloalkyl; cycloalkyl substituted by 1 to 3 substituents selected from the group consisting of alkoxyalkyl, alkyl, halogen, hydroxy, alkoxy, aryloxy, arylalkoxy, $-NR^1R^2$, $-NR^1C(O)R^2$, $-NR^1C(O)NR^1R^2$, $-NR^1C(O)OR^2$, $-NR^1S(O)_2R^2$, $-NR^1S(O)_2NR^1R^2$, $-C(O)OH$, $-C(O)OR^1$ and $-CONR^1R^2$; alkenyl; alkoxy; arylalkyl; arylalkenyl; heteroarylalkyl; heteroarylalkenyl; hydroxy; alkoxy; hydroxyalkyl; alkoxyalkyl; aminoalkyl; aryl; heteroaryl; thioalkyl and alkyl substituted by 1 to 3 subsituents selected from the group consisting of urea, sulfonamide, carboxamide, carboxylic acid, carboxylic ester and sulfonyl urea. Pharmaceutical compositions comprising at least one compound of formula I and a pharmaceutically acceptable carrier are also provided.

The compounds of the present invention can be useful as Thrombin receptor antagonists, also known as PAR-1 antagonists, or as cannabinoid (CB_2) receptor antagonists. Thrombin receptor antagonist compounds of the present invention can have anti-thrombotic, anti-platelet aggregation, anti-atherosclerotic, anti-restenotic anti-coagulant, and/or anti-inflammatory activity. CB_2 receptor inhibitor compounds of the present inventio can be useful for the treatment of rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, diabetes, osteoporosis, renal ischemia, cerebral stroke, cerebral ischemia, nephritis, inflammatory disorders of the lungs and gastrointestinal tract, and respiratory tract disorders such as reversible airway obstruction, chronic asthma and bronchitis.

Compounds of the invention can be useful for the treatment of thrombosis, atherosclerosis, restenosis, hypertension, angina pectoris, angiogenesis related disorders, arrhythmia, a cardiovascular or circulatory disease or condition, heart failure, acute coronary syndrome (ACS), myocardial infarction, glomerulonephritis, thrombotic stroke, thromboembolytic stroke, peripheral vascular diseases, deep vein thrombosis, venous thromboembolism, a cardiovascular disease associated with hormone replacement therapy, disseminated intravascular coagulation syndrome, cerebral infarction, migraine, erectile dysfunction, rheumatoid arthritis, rheumatism, astrogliosis, a fibrotic disorder of the liver, kidney, lung or intestinal tract, systemic lupus erythematosus, multiple sclerosis, osteoporosis, renal disease, acute renal failure, chronic renal failure, renal vascular homeostasis, renal ischemia, bladder inflammation, diabetes, diabetic neuropathy, cerebral stroke, cerebral ischemia, nephritis, cancer, melanoma, renal cell carcinoma, neuropathy, malignant tumors, neurodegenerative and/or neurotoxic diseases, conditions or injuries, Alzheimer's disease, an inflammatory disease or condition, asthma, glaucoma, macular degeneration, psoriasis, endothelial dysfunction disorders of the liver, kidney or lung, inflammatory disorders of the lungs and gastrointestinal tract, respiratory tract disease or condition, radiation fibrosis, endothelial dysfunction, periodontal diseases or wounds, or a spinal cord injury, or a symptom or result thereof, as well as other disorders in which thrombin and its receptor play a pathological role.

In particular, compounds of the present invention can be used to treat acute coronary syndrome, myocardial infarction ot thrombotic stroke.

Compounds of the present invention can also be used in a method to treat or prevent a condition associated with cardiopulmonary bypass surgery (CPB) comprising administering an effective amount of at least one thrombin receptor antagonist to a subject of said surgery. CPB surgery includes coronary artery bypass surgery (CABG), cardiac valvular repair and replacement surgery, pericardial and aortic repair surgeries. In particular, the present invention relates to a method of treating or preventing a condition associated with CABG surgery comprising administering an effective amount of at least one thrombin receptor antagonist to a subject of said surgery. The conditions associated with CABG are selected from the group consisting of: bleeding; thrombotic vascular events such as thrombosis, restenosis; vein graft failure; artery graft failure; atherosclerosis, angina pectoris; myocardial ischemia; acute coronary syndrome myocardial infarction; heart failure;

arrhythmia; hypertension; transient ischemic attack; cerebral function impairment; thromboembolic stroke; cerebral ischemia; cerebral infarction; thrombophlebitis; deep vein thrombosis; and, peripheral vascular disease.

In another embodiment, compounds of the present invention can be useful in a method for treating and/or preventing radiation- and/or chemical-induced toxicity in non-malignant tissue in a patient comprising administering a therapeutically effective amount of at least one compound of formula I. In particular, the radiation- and/or chemical-induced toxicity is one or more of intestinal fibrosis, pneumonitis, and mucositis. In a preferred embodiment, the radiation- and/or chemical-induced toxicity is intestinal fibrosis. In another preferred embodiment, the radiation- and/or chemical-induced toxicity is oral mucositis. In yet another embodiment, the radiation- and/or chemical-induced toxicity is intestinal mucositis, intestinal fibrosis, intestinal radiation syndrome, or pathophysiological manifestations of intestinal radiation exposure.

The present invention also provides methods for reducing structural radiation injury in a patient that will be exposed, is concurrently exposed, or was exposed to radiation and/or chemical toxicity, comprising administering a therapeutically effective amount of at least one compound of formula I. The present invention also provides methods for reducing inflammation in a patient that will be exposed, is concurrently exposed, or was exposed to radiation and/or chemical toxicity, comprising administering a therapeutically effective amount of at least one compound of formula I. The present invention also provides methods for adverse tissue remodeling in a patient that will be exposed, is concurrently exposed, or was exposed to radiation and/or chemical toxicity, comprising administering a therapeutically effective amount of at least one compound of formula I. The present invention also provides methods for reducing fibroproliferative tissue effects in a patient that will be exposed, is concurrently exposed, or was exposed to radiation and/or chemical toxicity, comprising administering a therapeutically effective amount of at least one compound of formula I.

The present invention further provides methods useful for treating a cell proliferative disorder in a patient suffering therefrom comprising administering a therapeutically effective amount of at least one compound of formula I. In one embodiment, the cell proliferative disorder is pancreatic cancer, glioma, ovarian cancer, colorectal and/or colon cancer, breast cancer, prostate cancer, thyroid cancer, lung cancer, melanoma, or stomach cancer. In one embodiment, the glioma

is an anaplastic astrocytoma. In another embodiment, the glioma is a glioblastoma multiforme.

As used above, the term inflammatory disease or condition includes irritable bowel syndrome, Crohn's disease, nephritis or a radiation- or chemotherapy- induced proliferative or inflammatory disorder of the gastrointestinal tract, lung, urinary bladder, gastrointestinal tract or other organ. The term respiratory tract disease or condition includes reversible airway obstruction, asthma, chronic asthma, bronchitis or chronic airways disease. "Cancer" includes renal cell carcinoma or an angiogenesis related disorder. "Neurodegenerative disease" includes Parkinson's disease, amyotropic lateral sclerosis, Alzheimer's disease, Huntington's disease or Wilson's disease.

Certain embodiments of this invention also relate to a method of using an effective amount of at least one compound of Formula I in combination with one or more additional agents for the treatment of thrombosis, atherosclerosis, restenosis, hypertension, angina pectoris, angiogenesis related disorders, arrhythmia, a cardiovascular or circulatory disease or condition, heart failure, acute coronary syndrome (ACS), myocardial infarction, glomerulonephritis, thrombotic stroke, thromboembolytic stroke, peripheral vascular diseases, deep vein thrombosis, venous thromboembolism, a cardiovascular disease associated with hormone replacement therapy, disseminated intravascular coagulation syndrome, cerebral infarction, migraine, erectile dysfunction, rheumatoid arthritis, rheumatism, astrogliosis, a fibrotic disorder of the liver, kidney, lung or intestinal tract, systemic lupus erythematosus, multiple sclerosis, osteoporosis, renal disease, acute renal failure, chronic renal failure, renal vascular homeostasis, renal ischemia, bladder inflammation, diabetes, diabetic neuropathy, cerebral stroke, cerebral ischemia, nephritis, cancer, melanoma, renal cell carcinoma, neuropathy, malignant tumors, neurodegenerative and/or neurotoxic diseases, conditions or injuries, Alzheimer's disease, an inflammatory disease or condition, asthma, glaucoma, macular degeneration, psoriasis, endothelial dysfunction disorders of the liver, kidney or lung, inflammatory disorders of the lungs and gastrointestinal tract, respiratory tract disease or condition, radiation fibrosis, endothelial dysfunction, periodontal diseases or wounds, or a spinal cord injury, or a symptom or result thereof. It is contemplated that a combination of this invention may be useful in treating more than one of the diseases listed.

For treating and/or preventing radiation- and/or chemical-induced toxicity in non-malignant tissue, the present invention includes administering to a patient in need of such treatment an effective amount of a combination of one or more compounds of formula I and one or more radiation-response modifiers selected from the group consisting of Kepivance™ (palifermin), L-glutamine, teduglutide, sucralfate mouth rinses, iseganan, lactoferrin, mesna and trefoil factor.

For treating a cell proliferative disorder the present invention includes administering to a patient in need of such tretment an effective amount of a combination of one or more compounds of formula I and another antineoplastic agent. In one embodiment, the other antineoplastic agent is temozolomide and the cell proliferative disorder is glioma. In another embodiment, the other antineoplastic agent is interferon and the cell proliferative disorder is melanoma. In one embodiment, the other antineoplastic agent is PEG-Intron (peginterferon alpha-2b) and the cell proliferative disorder is melanoma.

Pharmaceutical compositions comprising a therapeutically effective amount of a combination of at least one compound of formula I and at least one additional cardiovascular agent in a pharmaceutically acceptable carrier are also provided.

Pharmaceutical compositions comprising a therapeutically effective amount of a combination of at least one compound of formula I and a radiation-response modifier in a pharmaceutically acceptable carrier are also provided.

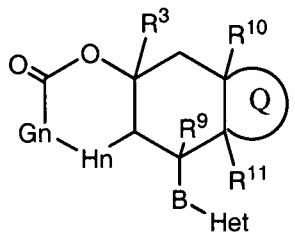
Pharmaceutical compositions comprising a therapeutically effective amount of a combination of at least one compound of formula I and an antineoplastic agent in a pharmaceutically acceptable carrier are also provided.

It is further contemplated that the combination of the invention can be provided as a kit comprising in a single package at least one compound of formula I in a pharmaceutical composition, and at least one separate pharmaceutical composition comprising a cardiovascular agent, a radiation-response modifier, or an antineoplastic agent.

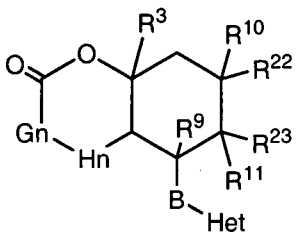
DETAILED DESCRIPTION:

In one embodiment, the present invention provides compounds represented by structural formula I, or pharmaceutically acceptable salt thereof, wherein the various moieties are as described as above.

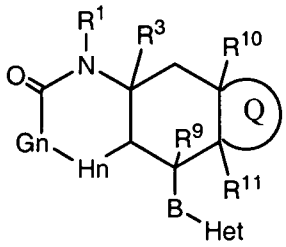
For compounds of Formula I, preferred embodiments of the compounds of formula I are as follows:



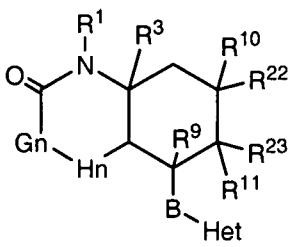
Ia



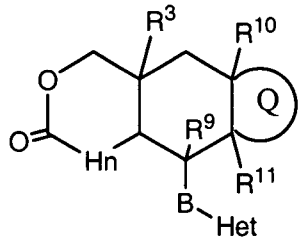
IIa



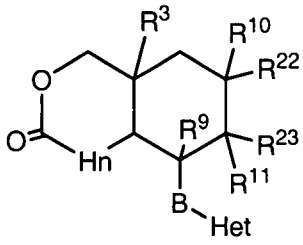
Ib



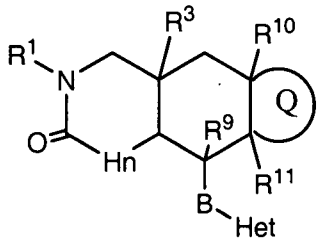
IIb



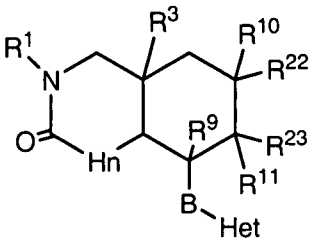
Ic



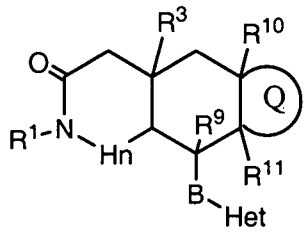
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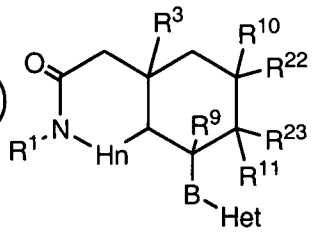
Id



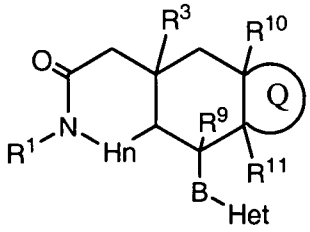
IId



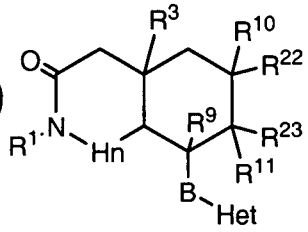
Ie



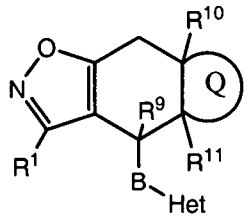
IIe



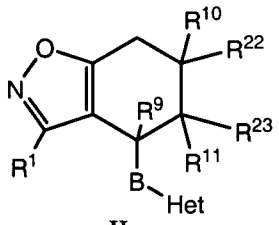
If



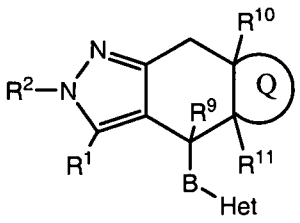
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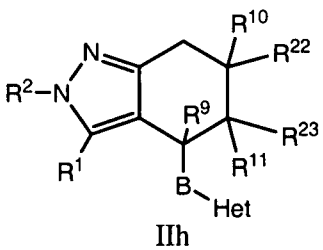
Ig



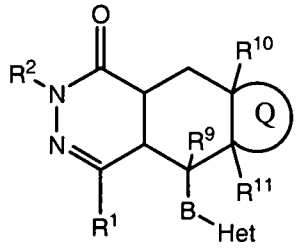
IIg



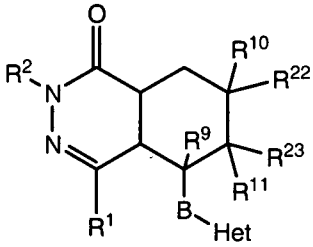
Ih



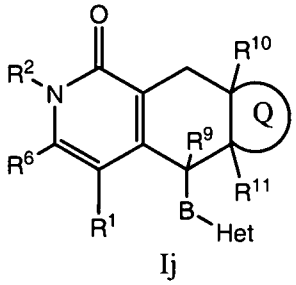
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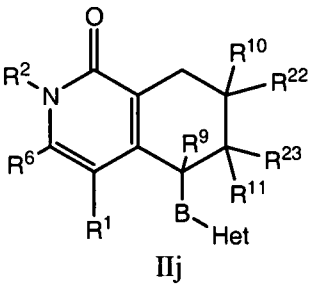
Ii



IIi

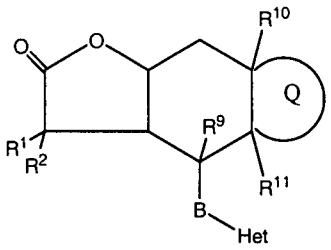


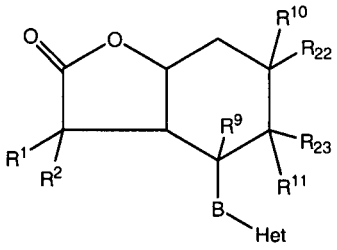
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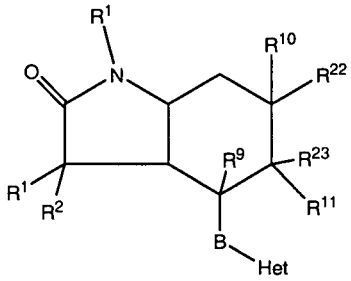


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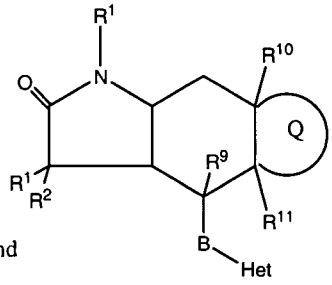
Additional preferred embodiments of the compounds of formula I are as follows:





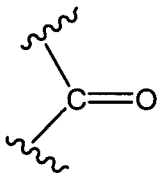


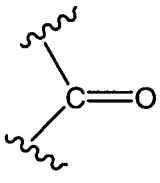
and



More preferred embodiments are those compounds of formula I where

E is -O-;

A is -O-,  or $-(CR^1R^2)-$;

G is  or $-(CR^1R^2)-$;

M is $-(CR^1R^2)-$;

X is –C(H)-;

R^3 is H;

R^9 is H;

R^{10} is H or alkyl;

R^{11} is H or alkyl;

R^{32} is H or alkyl;

R^{33} is H or alkyl;

B is $-CR^{12}=CR^{12a}-$;

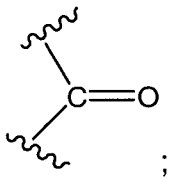
R^{12} and R^{12a} are H;

Het is aryl, aryl substituted by W, heteroaryl or heteroaryl substituted by W; and

W is aryl or aryl substituted with the 1 to 3 moieties comprising halogen, alkyl, $-CF_3$, -CN, -OH or -O-alkyl.

More preferred embodiments are those compounds of formula I where:

E is -O-;

A is  ;

G is $-CH_2-$;

X is –C(H)-;

R^3 is H;

R^9 is H;

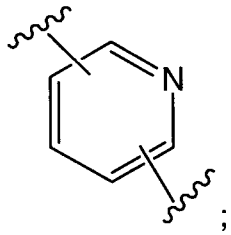
R^{10} is H or $-CH_3$;

R^{11} is H or $-CH_3$;

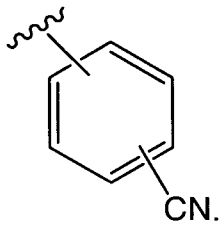
R^{32} is H or $-CH_3$;

R^{33} is H or $-CH_3$;

B is -CH=CH-;

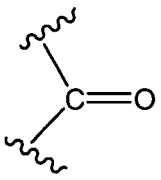
Het is  ;

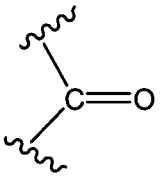
and

W is  .

In one embodiment of a compound of formula I wherein

E is -O-;

A is -O-,  or $-(CR^1R^2)-$;

G is  or $-(CR^1R^2)-$;

M is $-(CR^1R^2)-$;

X is –C(H)-;

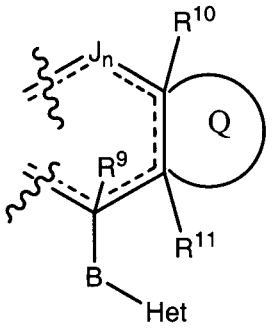
R^3 is H;

R^9 is H;

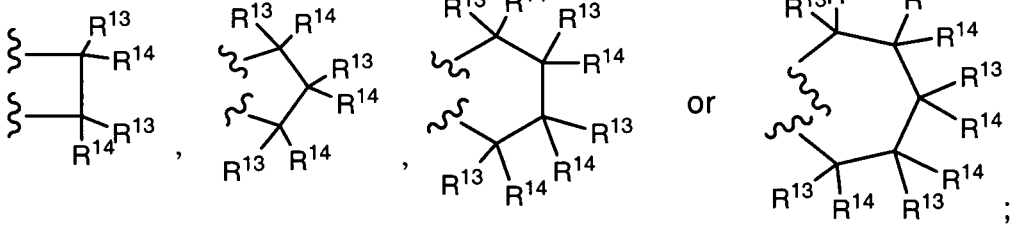
R^{10} is H or alkyl;

R^{11} is H or alkyl;

R^{32} and R^{33} are combined to form a ring structure Q, below



where Q is

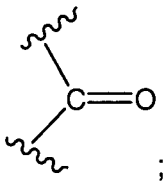


Het is aryl, aryl substituted by W, heteroaryl or heteroaryl substituted by W; and

W is aryl or aryl substituted with the 1 to 3 moieties comprising halogen, alkyl, $-CF_3$, -CN, -OH or -O-alkyl.

In an embodiment of a compound of formula I,

E is -O-;

A is  ;

G is $-CH_2-$;

X is –C(H)-;

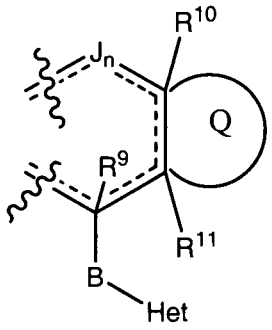
R^3 is H;

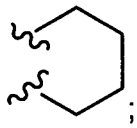
R^9 is H;

R^{10} is H or $-CH_3$;

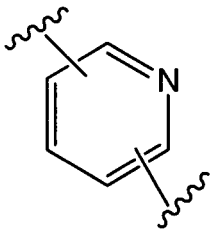
R^{11} is H or $-CH_3$;

R^{32} and R^{33} are combined to form a ring structure Q, below

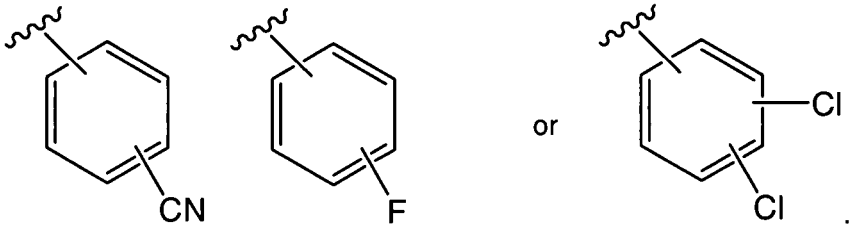


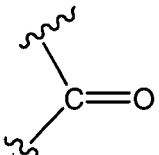
where Q is  ;

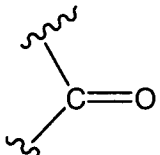
B is -CH=CH-;

Het is  ;

and

W is  .

A is –N(H)-, –N(alkyl)-,  or –(CR^{1}R^2)-;

G is  or –(CR^{1}R^2)-;

M is –(CR^{1}R^2)-;

X is –C(H)-;

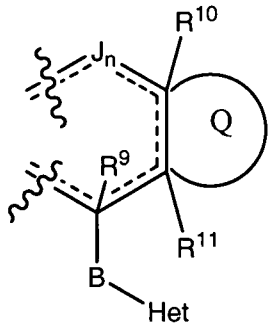
R^3 is H;

R^9 is H;

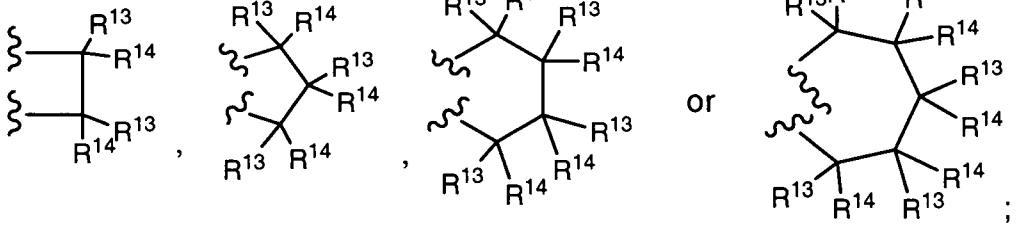
R^{10} is H or alkyl;

R^{11} is H or alkyl;

R^{32} and R^{33} are combined to form a ring structure Q, below



where Q is



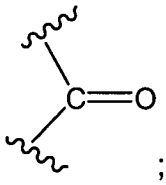
;

Het is aryl, aryl substituted by W, heteroaryl or heteroaryl substituted by W; and

W is aryl or aryl substituted with the 1 to 3 moieties comprising halogen, alkyl, -CF_3, -CN, -OH or -O-alkyl.

In another embodiment of a compound of formula I,

E is –N(H)- or –N(alkyl)-;

A is  ;

G is $-CH_2-$;

X is –C(H)-;

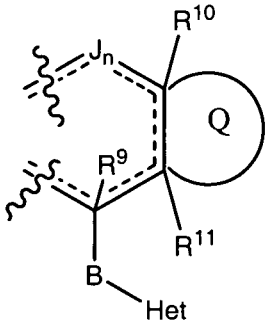
R^3 is H;

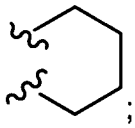
R^9 is H;

R^{10} is H or $-CH_3$;

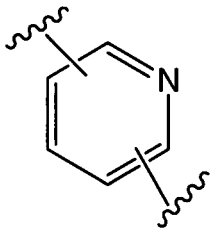
R^{11} is H or $-CH_3$;

R^{32} and R^{33} are combined to form a ring structure Q, below

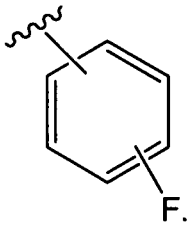


where Q is  ;

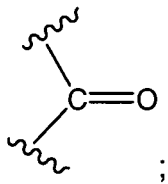
B is -CH=CH-;

Het is  ;

and

W is  F.

In another embodiment of a compound of formula I,

E is  ;

A is –N(H)-or –N(alkyl)-;

G is –N=;

M is $-(CR^1R^2)-$;

X is –C(H)-;

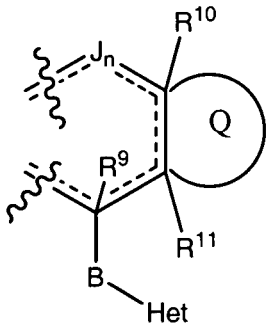
R^3 is H;

R^9 is H;

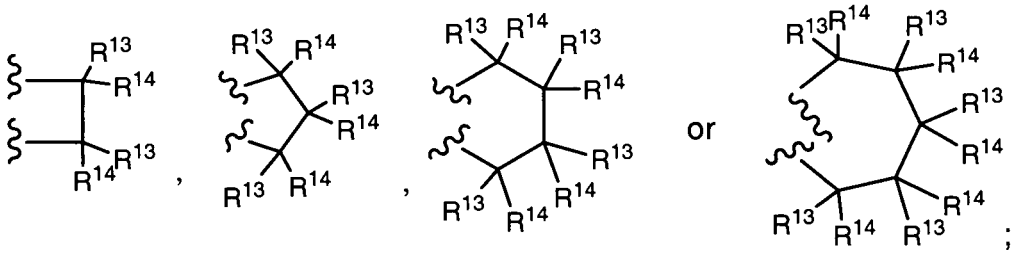
R^{10} is H or alkyl;

R^{11} is H or alkyl;

R^{32} and R^{33} are combined to form a ring structure Q, below



where Q is



;

Het is aryl, aryl substituted by W, heteroaryl or heteroaryl substituted by W; and

W is aryl or aryl substituted with the 1 to 3 moieties comprising halogen, alkyl, $-CF_3$, -CN, -OH or -O-alkyl.

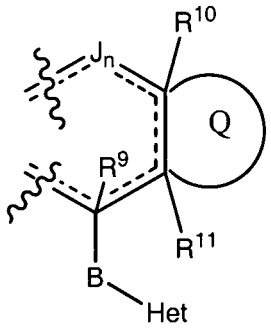
In another embodiment of a compound of formula I,

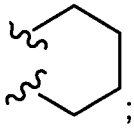
A is –N(H)-or $-N(CH_3)-$;

R^{10} is H or $-CH_3$;

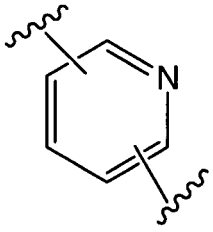
R^{11} is H or $-CH_3$;

R^{32} and R^{33} are combined to form a ring structure Q, below



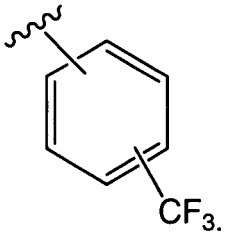
where Q is  ;

B is -CH=CH-;

Het is 

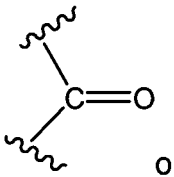
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and

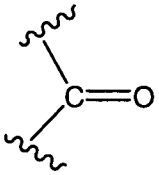
W is 

In another embodiment of a compound of formula I,

E is -O-;

A is -O-, 

or $-(CR^1R^2)-$;

G is 

or $-(CR^1R^2)-$;

M is $-(CR^1R^2)-$;

X is –C(H)–;

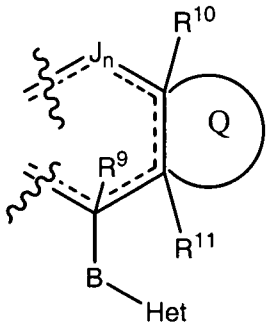
R^3 is H;

R^9 is H;

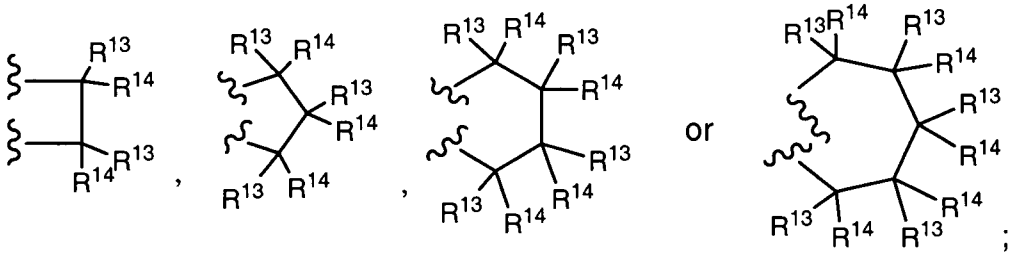
R^{10} is H or alkyl;

R^{11} is H or alkyl;

R^{32} and R^{33} are combined to form a ring structure Q, below



where Q is



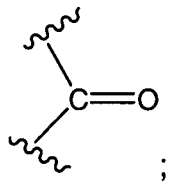
;

Het is aryl, aryl substituted by W, heteroaryl or heteroaryl substituted by W; and

W is aryl or aryl substituted with the 1 to 3 moieties comprising halogen, alkyl, $-CF_3$, -CN, -OH or -O-alkyl.

In an embodiment of a compound of formula I,

E is -O-;

A is 

;

G is $-CH(CH_3)-$;

X is –C(H)-;

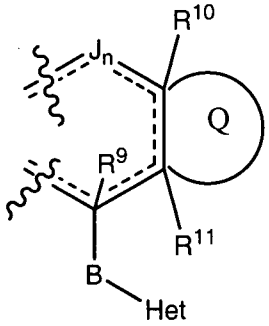
R^3 is H;

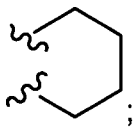
R^9 is H;

R^{10} is H or $-CH_3$;

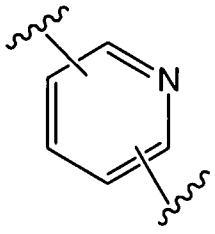
R^{11} is H or $-CH_3$;

R^{32} and R^{33} are combined to form a ring structure Q, below

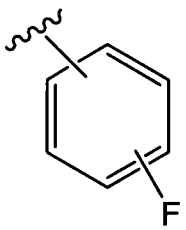
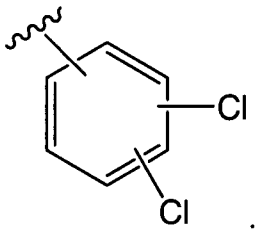


where Q is  ;

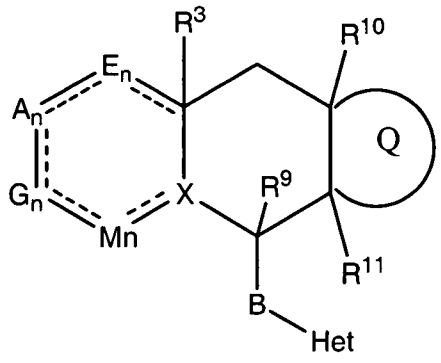
B is -CH=CH-;

Het is  ;

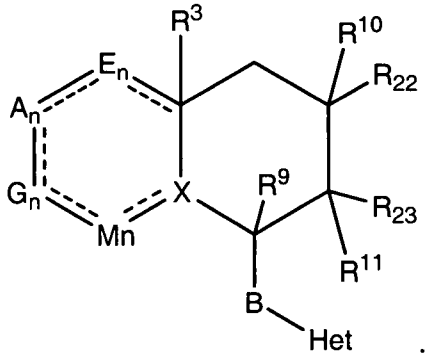
and

W is  or  .

For compounds of Formula I, further preferred embodiments are as follows:

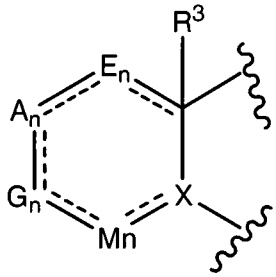


or

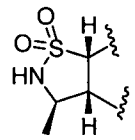
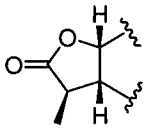
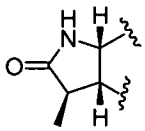
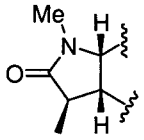
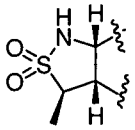
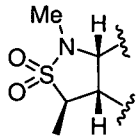
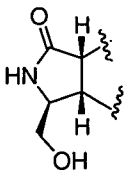
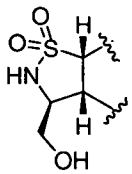
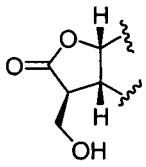
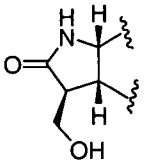
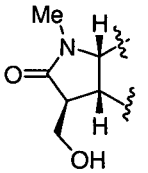
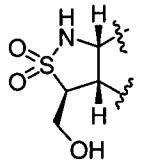
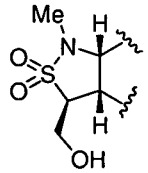


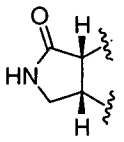
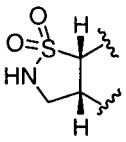
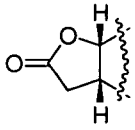
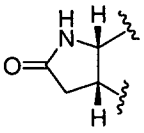
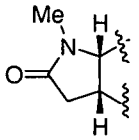
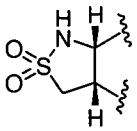
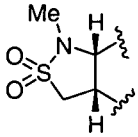
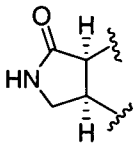
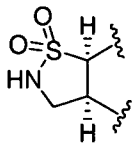
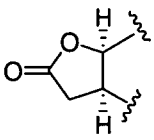
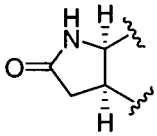
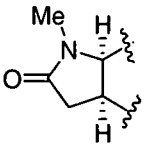
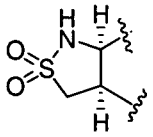
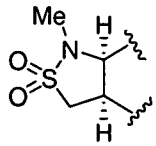
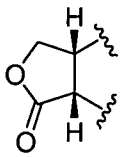
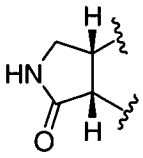
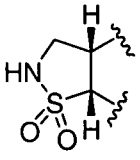
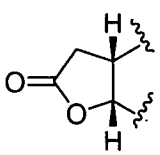
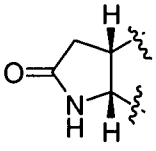
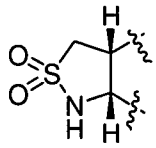
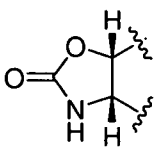
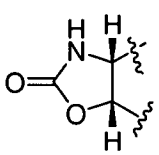
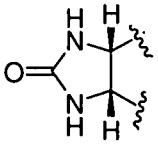
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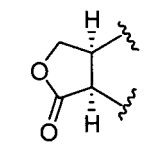
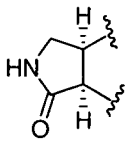
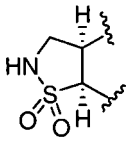
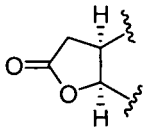
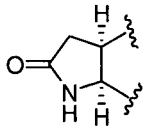
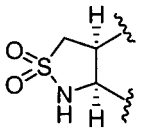
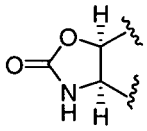
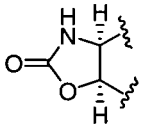
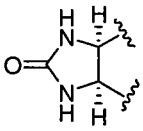
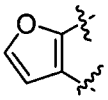
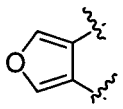
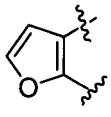
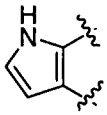
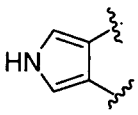
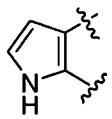
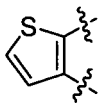
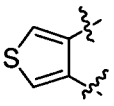
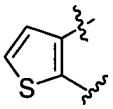
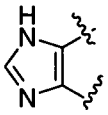
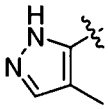
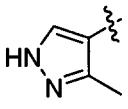
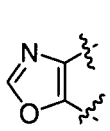
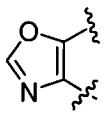
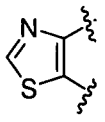
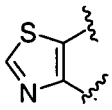
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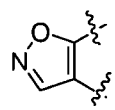
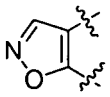
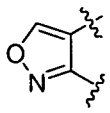
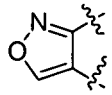
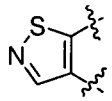
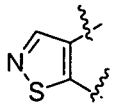
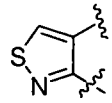
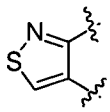
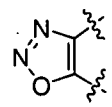
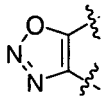
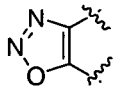
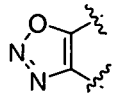
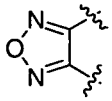
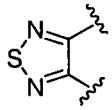
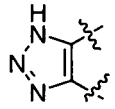
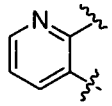
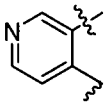
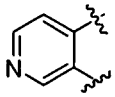
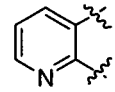
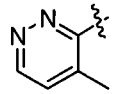
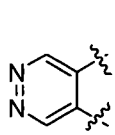
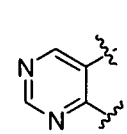
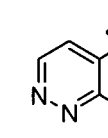


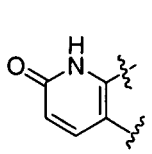
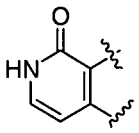
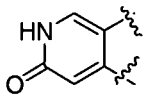
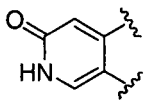
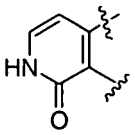
is















5




























5












or


In an embodiment of a compound of formula I,

R^3 is absent or R^3 is H;

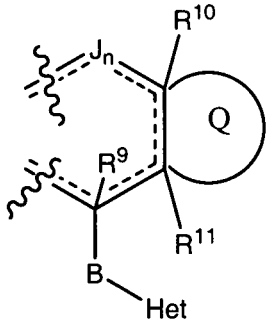
R^9 is H;

R^{10} is H or alkyl;

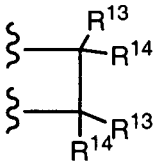
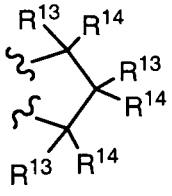
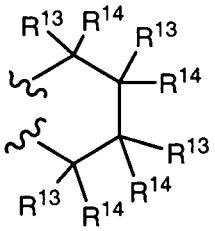
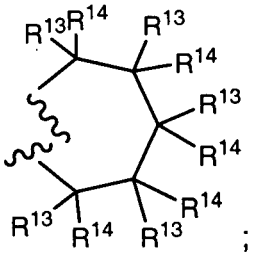
R^{11} is H or alkyl;

R^{32} is H or alkyl;

R^{33} is H or alkyl; or R^{32} and R^{33} are combined to form a ring structure Q, below



where Q is


,

,

or

;

B is -CH=CH-

Het is aryl, aryl substituted by W, heteroaryl or heteroaryl substituted by W; and

W is aryl or aryl substituted with the 1 to 3 moieties comprising halogen, alkyl, $-CF_3$, -CN, -OH or -O-alkyl.

In an additional embodiment of a compound of formula I,

R^3 is H;

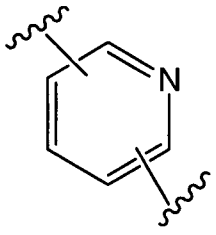
R^9 is H;

R^{10} is H or $-CH_3$;

R^{11} is H or $-CH_3$;

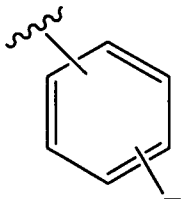
R^{32} is H or $-CH_3$;

R^{33} is H or $-CH_3$;

Het is 

;

and

W is 

.

In an embodiment of a compound of formula I,

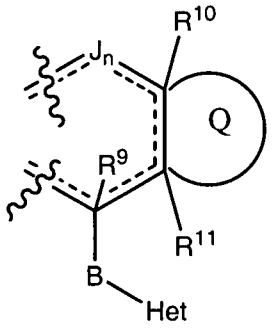
R^3 is absent or R^3 is H;

R^9 is H;

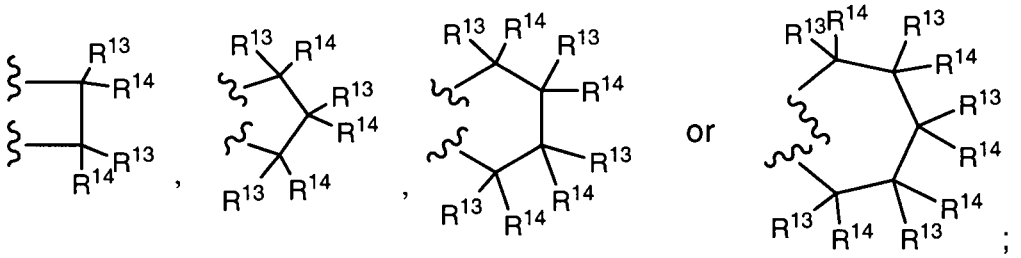
R^{10} is H;

R^{11} is H;

R^{32} and R^{33} are combined to form a ring structure Q, below



where Q is



R^{13} is $(-CH_2)_{n6}NHC(O)OR^{16b}$;

R^{16b} is alkyl;

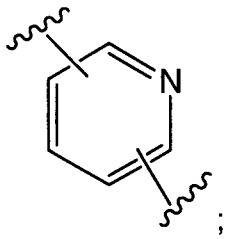
B is -CH=CH-

Het is aryl, aryl substituted by W, heteroaryl or heteroaryl substituted by W; and

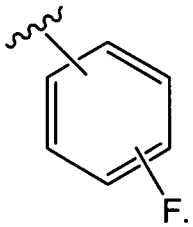
W is aryl or aryl substituted with the 1 to 3 moieties comprising halogen, alkyl, $-CF_3$, -CN, -OH or -O-alkyl.

In an embodiment of a compound of formula I,

R^{13} is $-NHC(O)OCH_2CH_3$;

Het is  ;

and

W is  F.

As used above, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"Patient" includes both human and animals.

"Subject" includes both mammals and non-mammalian animals.

"Mammal" means humans and other mammalian animals.

The following definitions apply regardless of whether a term is used by itself or in combination with other terms, unless otherwise indicated. Therefore, the definition

of "alkyl" applies to "alkyl" as well as the "alkyl" portions of "hydroxyalkyl", "haloalkyl", "alkoxy", etc.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched. The term "substituted alkyl" means that the alkyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), $-N(alkyl)_2$, carboxy and –C(O)O-alkyl. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, heptyl, nonyl, decyl, fluoromethyl, trifluoromethyl and cyclopropylmethyl.

"Aralkyl" or "arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl. The bond to the parent moiety is through the alkyl.

"Alkylaryl" means an alkyl-aryl- group in which the alkyl and aryl are as previously described. Preferred alkylaryls comprise a lower alkyl group. Non-limiting example of a suitable alkylaryl group is tolyl. The bond to the parent moiety is through the aryl.

"Alkenyl" means an aliphatic hydrocarbon group (straight or branched carbon chain) comprising one or more double bonds in the chain and which can be conjugated or unconjugated. Useful alkenyl groups can comprise 2 to about 15 carbon atoms in the chain, preferably 2 to about 12 carbon atoms in the chain, and more preferably 2 to about 6 carbon atoms in the chain. The alkenyl group can be substituted by one or more substituents independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, cyano and alkoxy. Non-limiting examples of suitable alkenyl groups include ethenyl, propenyl, n-butenyl, 3-methylbut-enyl and n-pentenyl.

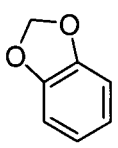
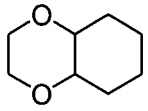
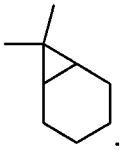
Where an alkyl or alkenyl chain joins two other variables and is therefore bivalent, the terms alkylene and alkenylene, respectively, are used.

"Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl, 3-methylbutynyl, n-pentynyl, and decynyl. The term "substituted alkynyl" means that the alkynyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of alkyl, aryl and cycloalkyl.

"Aryl" means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms. The aryl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Non-limiting examples of suitable aryl groups include phenyl, naphthyl, indenyl, tetrahydronaphthyl and indanyl. "Arylene" means a bivalent phenyl group, including ortho, meta and para-substitution.

"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, alkylaryl, heteroaralkyl, heteroarylalkenyl, heteroarylalkynyl, alkylheteroaryl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, heterocyclyl, -C(=N-CN)-NH_2, -C(=NH)-NH_2, -C(=NH)-NH(alkyl), Y_1Y_2N-, Y_1Y_2N-alkyl-, $Y_1Y_2NC(O)$-, $Y_1Y_2NSO_2$- and -$SO_2NY_1Y_2$, wherein Y_1 and Y_2 can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, and aralkyl. “Ring system substituent” may also mean a single moiety which simultaneously replaces two available

hydrogens on two adjacent carbon atoms (one H on each carbon) on a ring system. Examples of such moiety are methylene dioxy, ethylenedioxy, $-C(CH_3)_2-$ and the like which form moieties such as, for example:

  and  .

The term "Boc" refers to N-tert-butoxycarbonyl.

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalinyl, norbornyl, adamantyl and the like, as well as partially saturated species such as, for example, indanyl, tetrahydronaphthyl and the like.

"Cycloalkenyl" means a non-aromatic mono or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms which contains at least one carbon-carbon double bond. Preferred cycloalkenyl rings contain about 5 to about 7 ring atoms. The cycloalkenyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkenyls include cyclopentenyl, cyclohexenyl, cycloheptenyl, and the like. Non-limiting example of a suitable multicyclic cycloalkenyl is norbornylenyl.

"Cycloalkylene" refers to a corresponding bivalent ring, wherein the points of attachment to other groups include all positional isomers.

"Dihydroxyalkyl" refers to an alkyl chain substituted by two hydroxy groups on two different carbon atoms.

"Fluoroalkyl", "difluoroalkyl" and "trifluoroalkyl" mean alkyl chains wherein the terminal carbon is substituted by 1, 2 or 3 fluoroatoms, respectively, *e.g.*, $-CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$ or $-CH_2CH_2F$.

"Halo" refers to fluorine, chlorine, bromine or iodine radicals. Preferred are fluoro, chloro or bromo, and more preferred are fluoro and chloro.

"Halogen" means fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine and bromine.

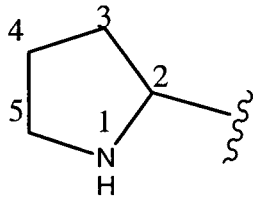
"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination, provided that the rings do not include adjacent oxygen and/or sulfur atoms. N-oxides of the ring nitrogens are also included, as well as compounds wherein a ring nitrogen is substituted by an alkyl group to form a quaternary amine. Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridone (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, oxadiazolyl, tetrazolyl, pyrimidyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, oxindolyl, naphthyridyl (*e.g.*, 1, 5 or 1,7), pyrido[2,3]imidazolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofuranyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzoxazolyl, benzothiazolyl, pyridopyrimidinyl, 7-azaindolyl and the like. The term "heteroaryl" also refers to partially saturated heteroaryl moieties such as, for example, tetrahydroisoquinolyl, tetrahydroquinolyl and the like. All positional isomers are contemplated, *e.g.*, 2-pyridyl, 3-pyridyl and 4-pyridyl.

The term "Het" is exemplified by the single ring, bicyclic and benzofused heteroaryl groups as defined immediately above. Het groups are joined to group B by a carbon ring member, *e.g.*, Het is 2-pyridyl, 3-pyridyl or 2-quinolyl. The Het ring can be substituted on any available ring carbon by a group W; 1 to 4 W substituents can be present on a Het ring.

"Heterocyclyl" or "heterocycloalkyl" means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the

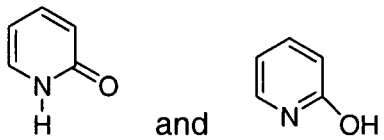
ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. Any –NH in a heterocyclyl ring may exist protected such as, for example, as an -N(Boc), -N(CBz), -N(Tos) group and the like; such protections are also considered part of this invention. The heterocyclyl can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxanyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiopyranyl, tetrahydrothiophenyl, lactam, lactone, and the like.

It should be noted that in hetero-atom containing ring systems of this invention, there are no hydroxyl groups on carbon atoms adjacent to a N, O or S, as well as there are no N or S groups on carbon adjacent to another heteroatom. Thus, for example, in the ring:



there is no -OH attached directly to carbons marked 2 and 5.

It should also be noted that tautomeric forms such as, for example, the moieties:



are considered equivalent in certain embodiments of this invention.

The term "heterospirocyclic" refers to a spirocyclic structure containing 3 to 5 carbon atoms and 1 or 2 heteroatoms selected from the group consisting of N, S and O, provided that the heteroatoms are not adjacent.

"Alkylamino" means an alkyl-amino group in which the alkyl group is as previously described. The bond to the parent moiety is through the amino.

"Alkylaminoalkyl" means an alkyl-amino-alkyl group in which the alkyl groups are as previously described. The bond to the parent moiety is through the alkyl.

"Alkylcycloalkylalkyl" means an alkyl-cycloalkyl-alkyl group in which the alkyl and cycloalkyl groups are as previously described. The bond to the parent moiety is through the alkyl.

"Alkylheteroaryl" means an alkyl-heteroaryl group in which the alkyl and heteroaryl groups are as previously described. The bond to the parent moiety is through the heteroaryl.

"Alkylheterocycloalkyl" means an alkyl-heterocycloalkyl group in which the alkyl and heterocycloalkyl groups are as previously described. The bond to the parent moiety is through the heterocycloalkyl group.

"Alkoxyalkyloxyalkyl" means an alkoxy-alkyl-O-alkyl group in which the alkoxy and alkyl groups are as previously described. The bond to the parent moiety is through the alkyl group.

"Alkynylalkyl" means an alkynyl-alkyl- group in which the alkynyl and alkyl are as previously described. Preferred alkynylalkyls contain a lower alkynyl and a lower alkyl group. The bond to the parent moiety is through the alkyl. Non-limiting examples of suitable alkynylalkyl groups include propargylmethyl.

"Haloalkyl" means a halo-alkyl- group in which the alkyl group is as previously described. The bond to the parent moiety is through the alkyl. Non-limiting examples of suitable haloalkyl groups include fluoromethyl and difluoromethyl.

"Heteroaralkyl" or "heteroarylalkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl are as previously described. Preferred heteroaralkyls contain a lower alkyl group. Non-limiting examples of suitable aralkyl groups include pyridylmethyl, and quinolin-3-ylmethyl. The bond to the parent moiety is through the alkyl.

"Heteroarylalkenyl" means a heteroaryl-alkenyl group in which the heteroaryl and alkenyl are as previously described. Preferred heteroarylalkenyl contain a lower alkenyl group. The bond to the parent moiety is through the alkenyl group.

"Heterocyclylalkyl" or "heterocycloalkylalkyl" means a heterocyclyl-alkyl group in which the heterocyclyl and alkyl groups are as previously described. The bond to the parent moiety is through the alkyl group.

"Heterocycloalkyloxy" means a heterocycloalkyl-O- group in which the heterocycloalkyl group is as previously described. The bond to the parent moiety is through the ether atom.

"Heteroarylalkoxyalkyl" means a heteroaryl-alkoxyalkyl group in which the heteroaryl and alkoxyalkyl groups are as described above. The bond to the parent moiety is through the alkyl group.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyls contain lower alkyl. Non-limiting examples of suitable hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Acyl" means an H-C(O)-, alkyl-C(O)- or cycloalkyl-C(O)-, group in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl and propanoyl.

"Aminoalkyl" means an amino-alkyl group in which the alkyl group is as previously described. The bond to the parent moiety is through the alkyl.

"Aroyl" means an aryl-C(O)- group in which the aryl group is as previously described. The bond to the parent moiety is through the carbonyl. Non-limiting examples of suitable groups include benzoyl and 1- naphthoyl.

"Alkenyloxy" means an alkenyl-O- group in which the alkenyl group is as previously described. The bond to the parent moiety is through the ether oxygen.

"Alkynyloxy" means an alkynyl-O- group in which the alkenyl group is as previously described. The bond to the parent moiety is through the ether oxygen.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy and n-butoxy. The bond to the parent moiety is through the ether oxygen.

"Aralkoxy" or "arylalkoxy" means an aralkyl-O- group in which the aralkyl group is as previously described. The bond to the parent moiety is through the oxygen atom.

"Alkoxyalkyl" or "alkyloxyalkyl" means an alkyl-O-alkyl group in which the alkyl and alkyl groups are as previously described. Non-limiting examples of suitable alkyloxyalkyl groups include methoxymethyl and ethoxymethyl. The bond to the parent moiety is through the alkyl group.

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Non-limiting examples of suitable aryloxy groups include phenoxy and naphthoxy. The bond to the parent moiety is through the ether oxygen.

"Aryloxyalkyl" means an aryl-O-alkyl group in which the aryl and alkyl groups are as previously described. Non-limiting examples of suitable aryloxyalkyl groups include phenoxymethyl and naphthoxymethyl. The bond to the parent moiety is through the alkyl group.

"Arylalkoxyalkyl" means an aryl-alkoxyalkyl group in which the aryl and alkoxyalkyl groups are as previously described. The bond to the parent moiety is through the alkyl group.

"Aralkyloxy" means an aralkyl-O- group in which the aralkyl group is as previously described. Non-limiting examples of suitable aralkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy. The bond to the parent moiety is through the ether oxygen.

"Arylalkenyl" means an aryl-alkenyl- group in which the aryl and alkenyl groups are as previously described. The bond to the parent moiety is through the alkenyl.

"Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkylthio groups include methylthio and ethylthio. The bond to the parent moiety is through the sulfur.

"Arylthio" means an aryl-S- group in which the aryl group is as previously described. Non-limiting examples of suitable arylthio groups include phenylthio and naphthylthio. The bond to the parent moiety is through the sulfur.

"Aralkylthio" means an aralkyl-S- group in which the aralkyl group is as previously described. Non-limiting example of a suitable aralkylthio group is benzylthio. The bond to the parent moiety is through the sulfur.

"Alkoxycarbonyl" means an alkyl-O-CO- group. Non-limiting examples of suitable alkoxycarbonyl groups include methoxycarbonyl and ethoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aryloxycarbonyl" means an aryl-O-C(O)- group. Non-limiting examples of suitable aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aralkoxycarbonyl" means an aralkyl-O-C(O)- group. Non-limiting example of a suitable aralkoxycarbonyl group is benzyloxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Alkylsulfonyl" means an alkyl-S(O_2)- group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the sulfonyl.

"Arylsulfonyl" means an aryl-S(O_2)- group. The bond to the parent moiety is through the sulfonyl.

"Cycloalkenyloxy" means a cycloalkenyl-O- group in which the cycloalkenyl group is as previously described. The bond to the parent moiety is through the ether atom.

"Cycloalkylyalkyl" means a cycloalkyl-alkyl group in which the cycloalkyl and alkyl groups are as previously described. The bond to the parent moiety is through the alkyl group.

"Cycloalkyloxy" or "cycloalkoxy" means a cycloalkyl-O- group in which the cycloalkyl group is as previously described. The bond to the parent moiety is through the ether atom.

"Cycloalkyloxyalkyl" means a cycloalkyl-O-alkyl group in which the cycloalkyl and alkyl groups are as previously described. The bond to the parent moiety is through the alkyl group.

"Haloalkoxyalkyl" means a halo alkoxyalkyl group in which the alkoxyalkyl group is as previously described. The bond to the parent moiety is through the alkyl group.

"Heterocyclylalkoxyalkyl" means a heterocyclyl-alkoxyalkyl group in which the alkoxyalkyl group is as previously described. The bond to the parent moiety is through the alkyl group.

The optional double bond represented by ----- means that at least a single bond must be present, but that a double bond can be present; when the double bond is present, R^{10} is absent.

When R^4 and R^5 join to form a ring with the nitrogen to which they are attached, the rings formed are 1-pyrrolidinyl, 1-piperidinyl and 1-piperazinyl, wherein the piperazinyl ring may also be substituted at the 4-position nitrogen by a group R^7.

The above statements, wherein, for example, R^4 and R^5 are said to be independently selected from a group of substituents, means that R^4 and R^5 are independently selected when attached to the same nitrogen, but also that where an R^4 or R^5 variable occurs more than once in a molecule, those occurrences are independently selected. Similarly, each occurrence of R^{13} or R^{14} is independent of

any other R^{13} or R^{14} in the same Q ring. Those skilled in the art will recognize that the size and nature of the substituent(s) will affect the number of substituents which can be present.

The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound' or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

The term "isolated" or "in isolated form" for a compound refers to the physical state of said compound after being isolated from a synthetic process or natural source or combination thereof. The term "purified" or "in purified form" for a compound refers to the physical state of said compound after being obtained from a purification process or processes described herein or well known to the skilled artisan, in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

The structure ----- in the compound of formula I, represents an optional double bond, the dotted line is a bond or no bond, resulting in a double bond or a single bond, as permitted by the valency requirement; with the proviso that R^3 is absent when the carbon to which R^3 would be attached is part of a double bond.

It should also be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and Tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene *et al*, *Protective Groups in organic Synthesis* (1991), Wiley, New York.

When any variable (e.g., aryl, heterocycle, R^2, etc.) occurs more than one time in any constituent or in Formula I, its definition on each occurrence is independent of its definition at every other occurrence.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

Prodrugs, solvates and co-crystals of the compounds of the invention are also contemplated herein. The term "prodrug", as employed herein, denotes a compound that is a drug precursor which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of Formula I or a salt and/or solvate thereof. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design,* (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press, both of which are incorporated herein by reference thereto.

"Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

A co-crystal is a crystalline superstructure formed by combining an active pharmaceutical intermediate with an inert molecule that produces crystallinity to the combined form. Co-crystals are often made between a dicarboxlyic acid such as fumaric acid, succinic acid etc. and a basic amine such as the one represented by compound I of this invention in different proportions depending on the nature of the co-crystal. (Rmenar, J. F. et. al. *J Am. Chem. Soc.* **2003**, *125*, 8456).

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective as thrombin

receptor antagonists and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect.

The compounds of Formula I can form salts which are also within the scope of this invention. Reference to a compound of Formula I herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formula I contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the compounds of the Formula I may be formed, for example, by reacting a compound of Formula I with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use.* (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents

such as lower alkyl halides (e.g. methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g. decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Compounds of Formula I, and salts, solvates, co-crystals and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates, co-crystals and prodrugs of the compounds as well as the salts and solvates, co-crystals of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate" "prodrug" and the like, is intended to equally apply to the salt, solvate and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

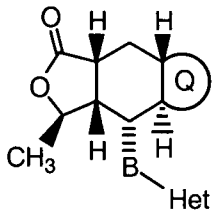
Polymorphic forms of the compounds of Formula I, and of the salts, solvates, co-crystals and prodrugs of the compounds of Formula I, are intended to be included in the present invention.

The compounds according to the invention have pharmacological properties; in particular, the compounds of Formula I can be nor-seco himbacine derivatives useful as thrombin receptor antagonists.

Compounds of the invention have at least one asymmetrical carbon atom and therefore all isomers, including enantiomers, stereoisomers, rotamers, tautomers and racemates of the compounds of Formula (I) (where they exist) are contemplated as being part of this invention. The invention includes d and l isomers in both pure form and in admixture, including racemic mixtures. Isomers can be prepared using conventional techniques, either by reacting optically pure or optically enriched starting materials or by separating isomers of a compound of Formula I. Isomers may also include geometric isomers, *e.g.*, when a double bond is present. Polymorphous forms of the compounds of Formula (I), whether crystalline or amorphous, also are contemplated as being part of this invention.

Those skilled in the art will appreciate that for some of the compounds of Formula I, one isomer will show greater pharmacological activity than other isomers.

Typical preferred compounds of the present invention have the following stereochemistry:



with compounds having that absolute stereochemistry being more preferred.

Those skilled in the art will appreciate that for some compounds of Formula I, one isomer will show greater pharmacological activity than other isomers.

Compounds of the present invention in which are generally prepared by processes in accordance with the following.

Some of the following below compounds, intermediates and processes, can be practiced by the methods as disclosed in any of US 6,063,847, US 6,326,380, US 6,645,987, U.S. Serial No. 10/271715, all of which are incorporated herein by reference

Following are examples of preparing starting materials and compounds of formula I. In the procedures, the following abbreviations are used:

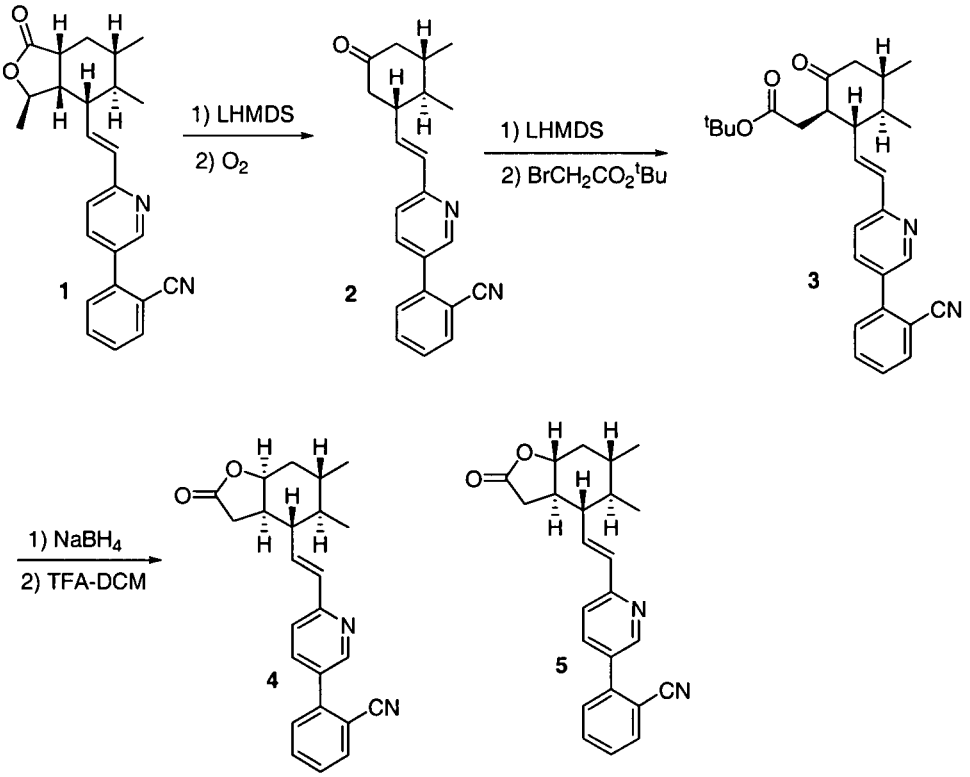
rt	room temperature
THF	tetrahydrofuran
Et_2O	ethyl ether
Me	methyl

Et	ethyl
EtOAc	ethyl acetate
$BnOCH_2Cl$	benzylchloromethylether
BuLi	Butyl Lithium
DBAD	Di-*tert*-butyl azodicarboxylate
DCE	1,2-dichloroethane
DCM	Dichloromethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Methyl sulfoxide
HATU	hexafluorophosphate
HOBT or HOBt	Hydroxybezotriazole
KHMDS	Potassium bis(trimethylsilyl)amide
LiHMDS or LHMDS:	Lithium bis(trimethylsilyl)amide
$NaB(O_2CCH_3)_3H$	Sodium triacetoxyborohydride
PhSeBr	Phenyl selenium bromide
PS	Polymer supported
PS-EDC	Polymer supported dimethyl aminopropyl ethylcarbodiimide hydrochloride
PS-NCO	Polymer supported isocyanate
PS-Tris-NH_2	Polymer supported trisamine
TFA	Trifluoroacetic acid
$Ti(OiPr)_4$	titanium isopropoxide;
TLC	thin layer chromatography
TMSI	Trimethylsilyl iodide or iodotrimethylsilane
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy, free radical
DIBAL, DIBALH	Diisobutylaluminum hydride
TIPSOTf	Triisopropylsilyl trifluoromethanesulfonate
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene

Synthesis

Lactones such as **4** and **5** can be prepared from the ketone **2** as described in scheme 1. The ketone was alkylated with *tert*-butyl bromoacetate to provide intermediate **3** which was reduced with sodium borohydride then cyclized to provide the *cis* and *trans* lactams **4** and **5**.

Scheme 1



Preparation of **2**

To a solution of **1** (9.0 g, 23.3 mmol) (see U.S. Patent 2004/0152736 A1 for the preparation of **1**) in 150 ml THF at 0 °C was added LHMDS as a 1M solution in THF (35 ml, 35 mmol, 1.5 eq.). The mixture was stirred for 30 min. then evacuated and filled with oxygen using a balloon. The mixture was stirred under the oxygen atmosphere for 30 min at 0 °C and 1 hr at rt. The reaction was quenched by the addition of aqueous sodium sulfite, stirred for 1 hr and extracted with ethyl acetate. The crude product obtained was purified by silica gel chromatography to obtain 300 mg of **2** as a minor product.

MS: 331.1 (MH^+)

Preparation of **3**

To a solution of **2** (160 mg, 0.48 mmol) in 5 ml THF at 0 °C was added a 1M solution of LHMDS in THF (0.58 ml, 058 mmol, 1.2 eq) and after stirring for 10 min, *tert*-buytl bromoacetate was added. The mixture was stirred overnight while allowing warming to rt. It was quenched by the addition of aqueous ammonium chloride, extracted with ethyl acetate and the crude product was purified by preparative TLC using 30% ethyl acetate in hexanes to provide 105 mg of **3**.

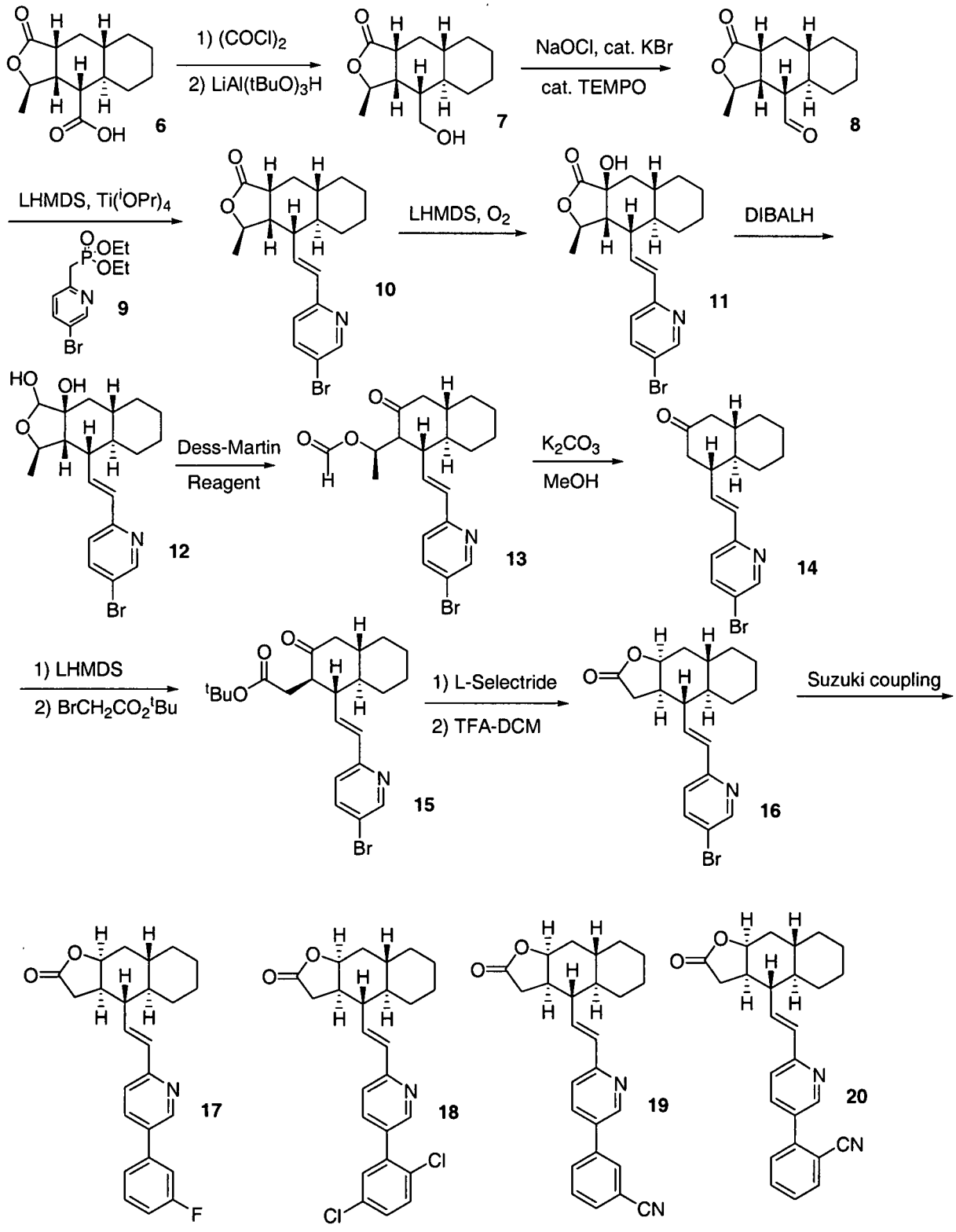
Preparation of **4** and **5**

To a solution of **3** (105 mg, 0.24 mmol) in 2 ml methanol at 0 °C was added $NaBH_4$ (9 mg, 0.24 mmol, 1.0 eq.) and stirred for 15 min. The reaction was quenched by the addition of aqueous ammonium chloride and extracted with ethyl acetate to give 80 mg of crude product. To a flask containing 55 mg of this crude product in 0.5 ml dichloromethane was added 0.5 ml of trifluoroacetic acid and stirred for 2 hr at rt. The solution was concentrated to dryness and the residue was taken in dichloromethane and washed with water followed by brine, dried over $MgSO_4$, concentrated and purified by preparative TLC using 30% ethyl acetate in hexanes to provide 14 mg of **4** and 24 mg of **5**.

MS for **4**: 373.1 (MH^+)
MS for **5**: 373.1 (MH^+)

An alternate approach to the preparation of these types of compounds is described in scheme 2. Carboxylic acid **6** was converted to the aldehyde **8** *via* the alcohol **7**. Horner-Wordsworth reaction with phosphonate **9** gave the vinyl pyridine **10** which was α-hydroxylated to **11**. Reduction of the lactone to the lactol followed by reaction with Dess-Martin periodinane reagent gave formate **13** which under basic conditions gave the ketone **14**. Alkylation with *tert*-butyl bromoacetate gave intermediate **15** which was reduced to the axial alcohol with L-selectride and cyclized to the lactone **16** under acidic conditions. Suzuki coupling of **16** gave the target compounds **17-20**.

Scheme 2



5 Preparation of **7**

To a solution of **6** (30 g, 0.119 mol) (see U.S. Patent 6063847 for the preparation of **6**) in 400 ml dichloromethane was added oxalyl chloride (21 ml, 0.241 mol, 2 eq.) followed by DMF (275 µl, 3.55 mmol, 5 mol%). The mixture was stirred for 2 hr, concentrated and evaporated with toluene to provide the acid chloride. This was dissolved in 500 ml THF, cooled to 0 °C, added lithium tri-*ter*-butoxyaluminohydride (76 g, 0.299 mol, 2.5 eq.) and the mixture was stirred for 2 hr. It was diluted with water, acidified with HCl, extracted with ethyl acetate to provide 21.6 g of **7**.

Preparation of **8**

To a solution of **7** (12.0 g, 50.4 mmol) in 200 ml dichloromethane at 0 °C was added 2,2,6,6-tetramethylpiperidinooxy (160 mg, 1.02 mmol, 2 mol%) and a solution of potassium bromide (600 mg, 5.04 mmol, 0.1 eq.) in 10 ml water. To this mixture was added drop by drop Clorox solution (92 g, ~6.15% NaOCl content) saturated with solid $NaHCO_3$. After the addition was complete, the mixture was stirred for 20 min, organic layer separated and the aqueous layer extracted with dichloromethane. The combined organic layer was washed with aq. $Na_2S_2O_3$, brine, dried over $MgSO_4$, filtered and concentrated to provide 12 g of **8** as a resin.

Preparation of **10**.

To a solution of **9** (20 g, 65 mmol) (see U.S. Patent 2004/0152736 A1 for the preparation of **9**) in 200 ml THF at 0 °C was added a 1M solution of LHMDS in THF (65 ml, 65 mmol) and the mixture stirred for 30 min at 0 °C. To this was added $Ti(O^iPr)_4$ (22.3 ml, 75.5 mmol) followed by a solution of aldehyde 8 (12 g) in 50 ml THF. The mixture was stirred for 15 min at 0 °C and 30 min at rt then quenched with aq. NH_4Cl. Ehtyl acetate extraction followed by chromatographic purification using 0% to 15% ethyl acetate-hexanes gave 3.3 g of **10**.

Preparation of **11**

To a solution of **10** (3.3 g, 8.46 mmol) in 50 ml THF at 0 °C was added a 1M solution of LHMDS in THF (12.7 ml, 12.7 mmol, 1.5 eq.) and stirred for 30 min. The flask was evacuated and filled with oxygen and stirred under the oxygen atmosphere for 1 hr at rt. It was quenched by the addition of aq. Na_2SO_3, stirred for 30 min. extracted with ethyl acetate and purified by chromatography using 0% to 20% ethyl acetate-hexanes to provide 3 g of **11**.

MS: 406.1 (MH^+)

Preparation of **12**

To a solution of **11** (4.2 g, 10.3 mmol) in 75 ml dichloromethane at -78 °C was added a 20 wt% solution of DIBALH in toluene (34.2 mmol, 41.4 mmol, 4 eq.) and stirred for 1 hr at -78 °C. It was quenched by the addition of aq. potassium sodium tartrate and extracted with dichloromethane to provide 2.89 g of **12**.

MS: 408.22 (MH^+)

Preparation of **13**

To a solution of **12** (2.89 g, 7.08 mmol) in 50 ml dichloromethane at rt was added $NaHCO_3$ (1.2 g, 14.28 mmol, 2 eq.) followed by Dess-Martin periodinane (3.90 g, 9.19 mmol, 1.3 eq.) and the suspension was stirred for 2 hr. The reaction mixture was diluted with ether and stirred with aq. $Na_2S_2O_3$ and $NaHCO_3$ until the two layers became clear. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layer was washed with aq. $Na_2S_2O_3$, $NaHCO_3$ mixture and brine. The solution was dried over $MgSO_4$, filtered, concentrated and evaporated to provide ~3.0 g of **13**.

MS: 406.2 (MH^+)

Preparation of **14**

A solution of **14** (~7.08 mmol) in 50 ml methanol was stirred with K_2CO_3 (3.9 g, 28.2 mmol, 4 eq.) at rt for 3 hr and diluted with water. It was extracted with ether and the crude product was chromatographed using 0% to 10% ethyl acetate – hexanes to provide 1.74 g of **14**.

MS: 334.1 (MH^+)

Preparation of **15**

To a solution of **14** (1.39 g, 4.15 mmol) in 30 ml THF at 0 °C was added a 1M solution of LHMDS in THF (5.0 ml, 5.0 mmol, 1.2 eq.) and stirred for 30 min then added *tert*-butyl bromoacetate (0.92 ml, 6.23 mmol, 1.5 eq.) and the mixture stirred overnight allowing to warm to rt. The solution was diluted with aq. NH_4Cl, extracted with ethyl acetate and the crude product was purified by chromatography to provide 920 mg of **15**.

MS: 448.1 (MH^+)

Preparation of **16**

To a solution of **15** (140 mg, 0.31 mmol) in 2.5ml THF at -78 °C was added 1M solution of L-selectride in THF (0.63 ml, 0.63 mmol, 2 eq) and the mixture stirred for 1 hr at -78°C. The reaction was quenched with the addition of 4 ml trifluoroacetic acid and stirred at rt for 1 hr, concentrated and suspended in aq. $NaHCO_3$. It was extracted with ethyl acetate and purified by chromatography using 0% to 20% ethyl acetate - hexanes to provide 70 mg of **16**.

MS: 376.1 (MH^+)

Preparation of **17**

A solution of **16** (20 mg, 0.053 mmol), *m*-fluorophenylboronic acid (11.2 mg, 0.08 mmol, 1.5 eq.), K_2CO_3 (30 mg, 0.217 mmol, 4 eq.) and $Pd(PPh_3)_4$ (3.1 mg, 2.7 μmol, 5 mol) in a mixture of 1 ml toluene, 0.5ml ethanol and 0.3 ml water was bubbled with argon and heated in a sealed tube at 100 °C for 1 hr. After aqueous work-up, the crude product was purified by preparative TLC using 20% ethyl acetate-hexanes to provide 14 mg of **17**.

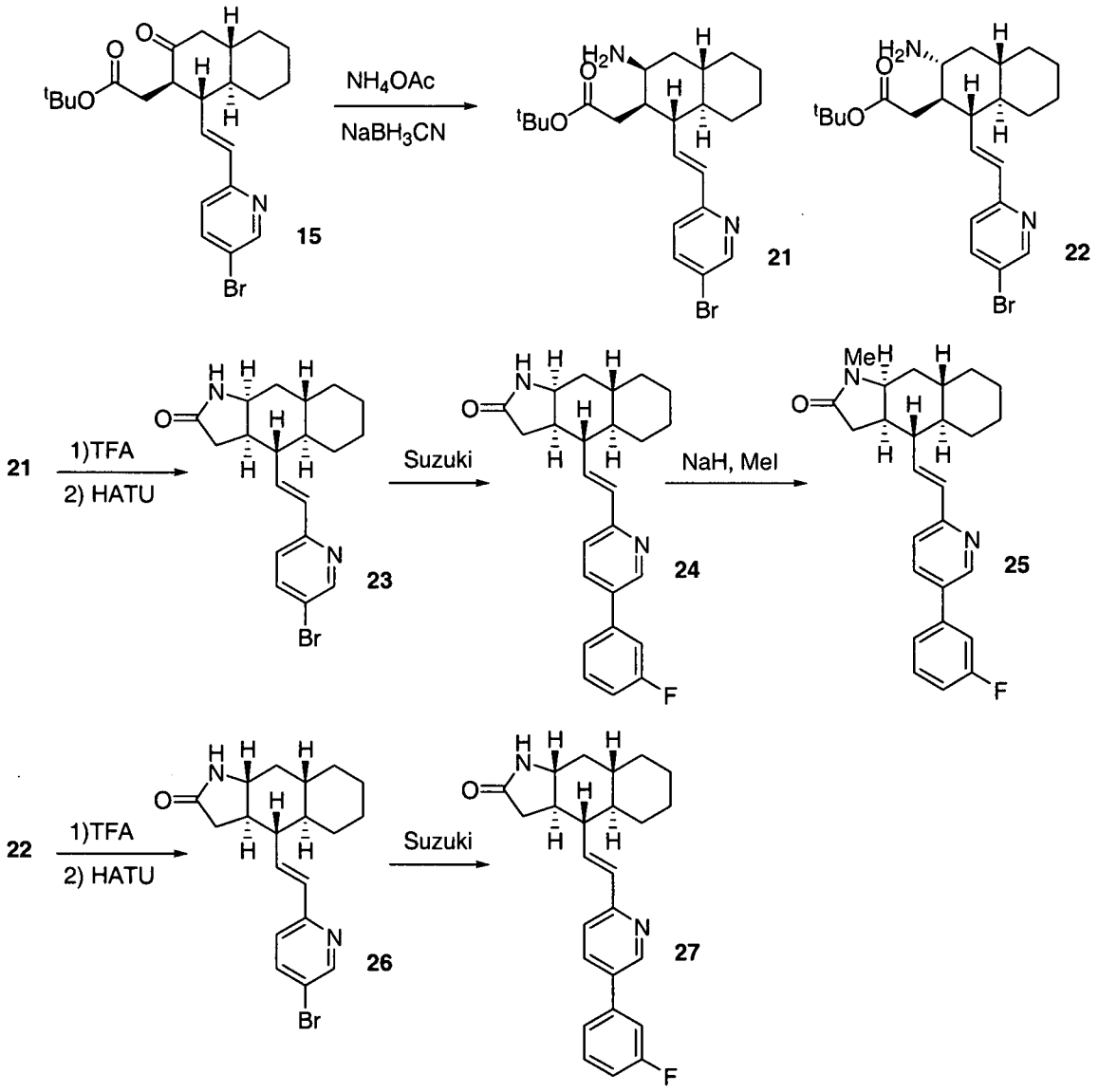
MS: 392.1 (MH^+)

Compounds **18**, **19** and **20** were prepared using an analogous procedure.

MS for **18**: 442.1 (MH^+)
MS for **19**: 399.2 (MH^+)
MS for **20**: 399.2 (MH^+)

The lactam analogs were prepared as described in scheme 3. Reductive amination of ketone **15** gave a mixture of axial and equatorial amines **21** and **22**. Cleavage of the *tert*-butyl ester of **21** was achieved with trifluoro acetic acid and the resultant amino acid was treated with HATU to provide the *cis* lactam **23.** Suzuki coupling gave **24** which on N-methylation gave **25**. Similarly, the equatorial amine **22** was converted to the *trans*-lactam **27**.

Scheme 3



Preparation of **21** and **22**

To a solution of **15** (300 mg, 0.67 mmol), in 5ml methanol and 1 ml dichloromethane was added ammonium acetate (515 mg, 6.68 mmol, 10 eq.), 3Å molecular sieves (~600 mg) and sodium cyanoborohydride (42 mg, 0.668 mmol, 1 eq.) and the mixture stirred at rt for 2 days. It was poured into aqueous sodium bicarbonate, extracted with dichloromethane and purified by chromatography using 3% 7N ammonia-methanol solution in dichloromethane to provide 150 mg of **21** and 58 mg of **22**.

MS for **21**: 449.1 (MH^+)
MS for **22**: 449.1 (MH^+)

Preparation of **23**

A solution of **21** (150 mg) in 1 ml dichloromethane and 3 ml trifluoroacetic acid was stirred at rt for 2 hr, concentrated and evaporated with n-heptane to provide the acid. To a solution of this product in 4 ml DMF at rt was added triethylamine (0.19 ml, 1.36 mmol, 4 eq.) followed by HATU (255 mg, 0.67 mmol, 2 eq.) and the mixture was stirred overnight at rt. It was diluted with ethyl acetate and washed aq. sodium bicarbonate, brine, dried over $MgSO_4$, filtered and concentrated. The crude product was chromatographed with 0% to 80% ethyl acetate – hexanes to provide 55 mg of **23**.

MS: 375.1 (MH^+)

Preparation of **24**

A solution of **23** (55 mg, 0.147 mmol), 3-fluorophenylboronic acid (31 mg, 0.22 mmol, 1.5 eq.), $Pd(PPh_3)_4$ (8.5 mg, 7.4 μmol, 5 mol%) and K_2CO_3 (81 mg, 0.586 mmol, 4 eq.) in a mixture of toluene (1ml), ethanol (0.5 ml) and water (0.3 ml) in a sealed tube was bubbled with argon and heated at 100 °C for 5 hr. It was poured into water, extracted with ethyl acetate and purified by preparative TLC using 3%methanol – dichloromethane mixture to provide 44 mg of **24**.

MS: 391.2 (MH^+)

Preparation of **25**

To a solution of **24** (22 mg, 0.056 mmol) in 1ml DMF at rt was added sodium hydride (12 mg of 60% dispersion in mineral oil, 0.30 mmol, 5 eq.) followed by iodomethane (0.026 ml, 0.28 mmol, 5 eq.) and the mixture stirred for 2.5 hr at rt. It was poured into aq. ammonium chloride, extracted with ethyl acetate and purified by preparative TLC using 80% ethyl acetate – hexanes to provide 9 mg of **25**.

MS: 405.1 (MH^+)

Preparation of **26**

A solution of **22** (55 mg) in 1ml dichloromethane and 3 ml trifluoroacetic acid was stirred at rt for 1 hr, concentrated and evaporated with n-heptane to provide the acid. To a solution of this acid in 2 ml DMF was added triethylamine (0.070 ml, 0.50 mmol, 4 eq) followed by HATU (93 mg, 0.25 mmol, 2 eq) and stirred overnight at rt. It was diluted with ethyl acetate, washed with aq. sodium bicarbonate, brine, dried over $MgSO_4$ and purified by chromatography using 3% methanol-dichloromethane to provide 35 mg of **26**.

MS: 375.1 (MH^+)

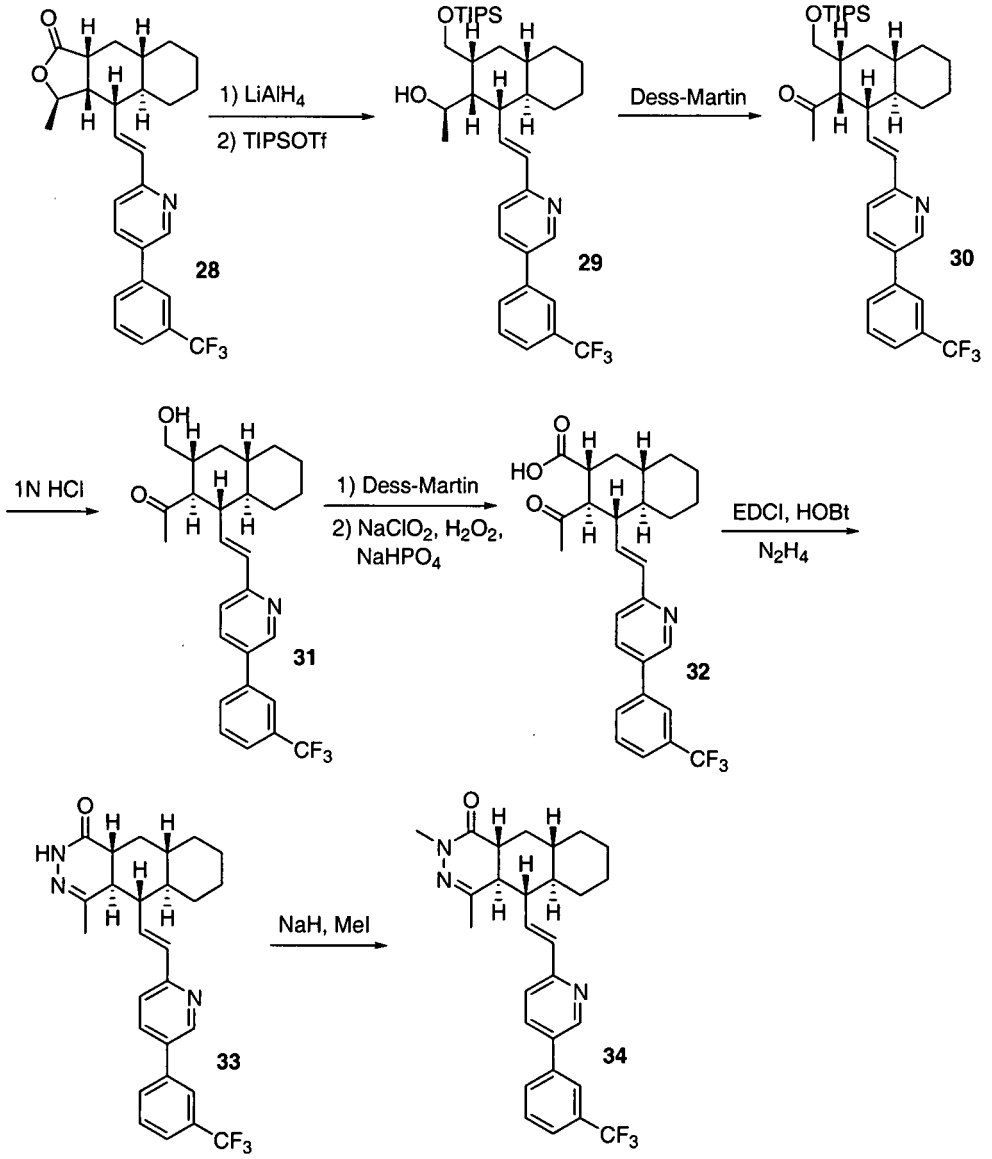
Preparation of **27**

A solution of **22** (35 mg, 0.093 mmol), 3-fluorophenylboronic acid (20 mg, 0.14 mmol, 1.5 eq.), $Pd(PPh_3)_4$ (6 mg, 5.2 μmol, 6 mol%) and K_2CO_3 (52 mg, 0.38 mmol, 4 eq.) in a mixture of toluene (1ml), ethanol (0.5 ml) and water (0.3 ml) in a sealed tube was bubbled with argon and heated at 100 °C for 5 hr. It was poured into water, extracted with ethyl acetate and purified by preparative TLC using 3%methanol – dichloromethane mixture to provide 26 mg of **27**.

MS: 391.2 (MH^+)

Preparation of phthalazinone type analogs are shown in scheme 4. Lactone **28** was reduced to the diol and the primary alcohol was protected to provide **29**. Dess-Martin oxidation followed by treatment with 1N HCl gave alcohol **31** which was oxidized to the carboxylic acid **32**. Coupling of this acid with hydrazine gave **33** which on N-methylation gave **34**.

Scheme 4



Preparation of **30**

To a solution of **28** (2.0 g, 4.39 mmol) (see U.S. Patent 6063847 for the preparation of **28**) in 20 ml THF at rt was added 1M $LiAlH_4$ solution in THF (4.4 ml, 4.4 mmol, 1 eq.) and stirred at rt for 1 hr. It was quenched by the addition of small amount of ethyl acetate, concentrated under vacuum and poured into water. The slurry was acidified with dilute sulfuric acid and extracted 3x with dichloromethane. The combined organic layer was washed with water, aq. sodium bicarbonate, brine, dried over $MgSO_4$, filtered and concentrated to provide the diol.

To a solution of this diol and triethyl amine (0.92 ml, 6.60 mmol, 1.5 eq.) in 30 ml dichloromethane at -40 °C was added triisopropylsilyl trifluoromethanesulfonate (1.3 ml, 4.84 mmol, 1.1 eq.) and stirred for 1 hr while allowing the solution to warm up to 0 °C. The mixture was diluted with ether, washed with aq. sodium bicarbonate and brine. It was dried over $MgSO_4$, filtered and concentrated to provide crude **29**.

To a solution of above crude **29** in 30 ml dichloromethane at was added $NaHCO_3$ (1.85 g, 22.02 mmol) and Dess-Martin periodinane (2.1 g, 5.29 mmol) and stirred for 1 hr. It was diluted with ether, added aqueous solution of $Na_2S_2O_3$ and $NaHCO_3$, stirred vigorously and the organic layer separated. The aqueous phase was extracted with ether and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered, concentrated and chromatographed with 0% to 10% ethyl acetate-hexane to provide 1.83 g of **30**.

Preparation of **31**

To a solution of **30** (1.05 g, 1.71 mmol) in 10 ml THF at rt was added 0.85 ml of con. HCl and the mixture stirred for 2 hr. It was poured into aq. $NaHCO_3$ solution and extracted 3x with ethyl acetate. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, concentrated and chromatographed with 0% to 50% ethyl acetate-hexanes to provide 0.70 g of **31**.

MS: 458.1 (MH^+)

Preparation of **32**

To a solution of **31** (530 mg, 1.16 mmol) in 10 ml dichloromethane at rt was added $NaHCO_3$ (195 mg, 2.32 mmol, 2 eq.) and Dess-Martin periodinane (550 mg, 1.39 mmol, 1.2 eq.) and the mixture was stirred at rt for 2 hr. It was diluted with ether and stirred vigorously with an aqueous solution of $Na_2S_2O_3$ and $NaHCO_3$ for 30 min. The organic layer was separated and the aqueous layer was extracted 2x with ether. The combined organic layer was washed with an aqueous solution of $Na_2S_2O_{34}$ and $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated to provide the crude aldehyde.

To a solution of this aldehyde in 3 ml THF and 7 ml acetonitrile was added aqueous hydrogen peroxide solution (0.13 ml of 30% solution, 1.26 mmol, 1.1 eq) and NaH_2PO_4 (35 mg, 0.29 mmol, 0.25 eq.). To this mixture was added a solution of $NaClO_2$ (185 mg of 80% solid, 1.64 mmol, 1.4 eq) in 3 ml water. After stirring for 1 hr at rt, the solution was diluted with water and extracted 3x with dichloromethane. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated to provide 490 mg of **32**.

MS: 472.1 (MH^+)

Preparation of **33**

To a suspension of **32** (0.49 g, 1.04 mmol) in 10 ml acetonitrile and 5 ml DMF was added HOBt (0.17 g, 1.26 mmol, 1.2 eq) followed by EDCI (0.24 g, 1.25 mmol, 1.2 eq.) and 5 ml dichloromethane. The solution was stirred for 1 ht at rt then cooled to 0 °C and transferred to another flask containing a solution of hydrazine (65 µl, 2.07 mmol, 2 eq.) and cyclohexene (100 µl) in 5 ml acetonitrile kept at 0 °C. The mixture was stirred for 30 min, diluted with ethyl acetate, washed 3x with aq. $NaHCO_3$, brine, dried over $MgSO_4$, filtered, concentrated and chromatographed with 50% ethyl acetate-hexanes to provide 280 mg of **33**.

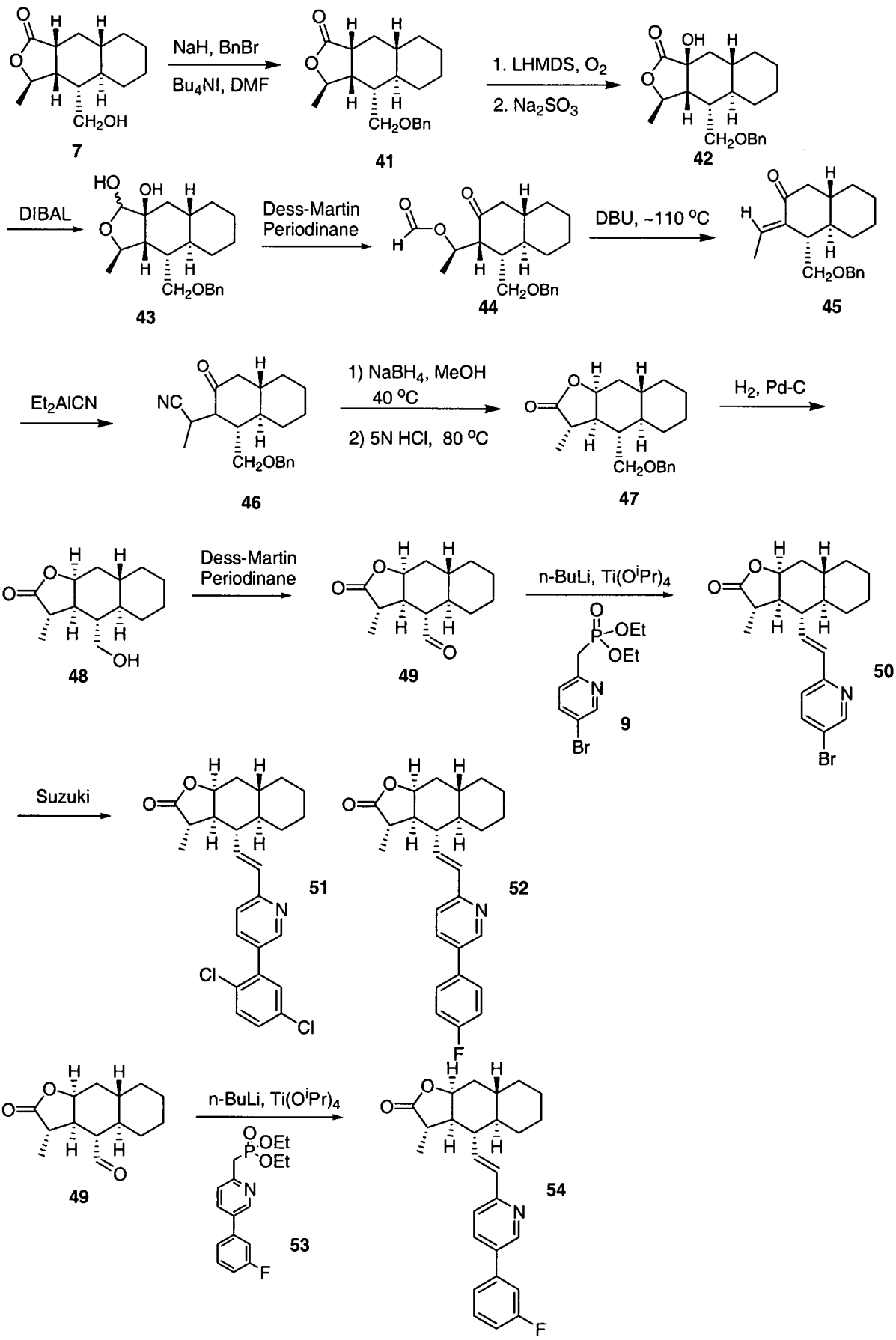
MS: 468.1 (MH^+)

Preparation of **34**

To a solution of **33** (180 mg, 0.39 mmol) in 3 ml DMF at rt was added NaH (23 mg of 60% dispersion in mineral oil, 0.87 mmol, 1.5 eq.) and iodomethane (36 µl, 0.58 mmol, 1.5 eq.). The mixture was stirred for 3 hr, added aq. ammonium chloride and extracted 3x with ethyl acetate. The combine organic layer washed 2x with water, brine, dried over $MgSO_4$, filtered, concentrated and chromatographed with 0% to 25% ethyl acetate – hexanes to provide 170 mg of **34**.

MS: 482.1 (MH^+)

Another alternative preparation of isolactone analogs is presented below. Alcohol **7** was protected as benzyl ether and α-oxygenated to provide **42**. Dibal reduction followed by Dess-Martin reaction gave formate **44** which was converted to enone **45**. Conjugate addition of cyanide followed by reduction and hydrolysis gave lactone **47** which was converted to targets **51**, **52** and **54**.


NaH, BnBr
Bu4NI, DMF
1. LHMDS, O2
2. Na2SO3
DIBAL
Dess-Martin Periodinane
DBU, ~110 °C
Et2AlCN
1) NaBH4, MeOH
40 °C
2) 5N HCl, 80 °C
H2, Pd-C
Dess-Martin Periodinane
n-BuLi, Ti(OiPr)4
Suzuki
n-BuLi, Ti(OiPr)4
7
41
42
43
44
45
46
47
48
49
9
50
51
52
53
54

Preparation of **41**

Sodium hydride (840 mg, 21 mmol) was added to a stirred solution of **7** (2.0g, 8.4 mmol) and Bu_4NI (930mg, 2.6mmol) in DMF at 0°C under N_2. The mixture was stirred for 30 minutes and brought to room temperature. Benzyl bromide (2.5 mL, 21 mmol) was added drop wise to the above mixture and stirred at room temperature for another 2.5 hours. The mixture was poured into a sat. NH_4Cl solution and extracted with ethyl ether. The combined organic extracts were washed with H_2O, brine and dried over $MgSO_4$. The crude residue was purified *via* silica gel column chromatography (ethyl acetate / Hexane 10:90) to give compound **41** (2.6g, 7.9mmol, 96%).

Preparation of **42**

To a solution of **41** (100mg, 0.31mmol) in THF (2ml) at 0°C under Argon was added LiHMDS (0.92 mL, 1M in THF solution). The mixture was brought to room temperature and stirred for 30minutes then under oxygen atmosphere for over 2 hours. Na_2SO_3 (6mL) was added to the mixture and stirred for 30minutes. The organic layer was extracted with ethyl acetate and CH_2Cl_2. The combined extracts were dried over $MgSO_4$. The crude product was purified *via* flash chromatography (ethyl acetate / Hexane 5:95) and evaporated to give **42** (58mg, 0.17mmol, 55%).

Preparation of **43**

To a solution of **42** (647mg, 1.9mmol) in CH_2Cl_2 (6mL) at -78°C under N_2 was added DIBAL drop wise and the mixture was slowly brought to room temperature. After 3 hours of stirring the mixture was diluted with ethyl acetate and poured into sat. sodium potassium tartrate. The organic layer was extracted with ethyl acetate then CH_2Cl_2. The combined extracts were dried over $MgSO_4$ to give crude material **43** (651mg).

Preparation of **44**

To a solution of **43** (2.42 g, 7.0 mmol) in CH_2Cl_2 (70 mL) at 0 °C under N_2 was added Dess-Martin periodinane (4.5g, 10.5mmol). The mixture was stirred for 1 hour and slowly brought to room temperature. After 2 hours of stirring, Sat. $Na_2S_2O_3$ (100 mL) was added and stirred for 10 minutes then Sat. $NaHCO_3$ (100 mL) was added. About 45 minutes of stirring, the organic layer was extracted with ethyl acetate then CH_2Cl_2. The combined extracts were dried over $MgSO_4$ and evaporated to give compound **44** (2.21g, 6.4mmol, 92%).

Preparation of **45**

DBU (1.2 ml, 2.61 mmol) was added drop wise to a solution of **44** in toluene (30 mL) and heated at 110 °C for 2 hours. The mixture was diluted with CH_2Cl_2 and washed with $NaHCO_3$ then H_2O. The organic layer was dried over $MgSO_4$ and evaporated. The crude residue was purified via flash chromatography (Ethyl acetate / Hexane, 5:95) to give **45** (1.5g, 5.0mmol, 78%).

Preparation of **46**

To a stirring solution of **45** (20mg, 0.7mmol) in toluene (2.0mL) at room temperature was added diethylaluminum cyanide (0.31mL, 0.31mmol) and stirred for 3 hours. The mixture was diluted with ethyl acetate and poured into a solution of sat. sodium potassium tartrate. The organic layer was extracted with ethyl acetate then CH_2Cl_2. The combined extracts were dried over $MgSO_4$ and concentrated. The resulting residue was purified *via* flash chromatography (Ethyl acetate / Hexane, 5:95) to give compound **46** (17mg, 0.05mmol, 79%).

Preparation of **47**

Sodium borohydride (755 mg, 19.97 mmol) was added to a solution of **46** (775mg, 2.3mmol) in MeOH (60 mL) and heated at 40 °C for 1.5 hour. After the solution was brought to room temperature, 5N HCl (75mL) was added and the mixture heated for another 4 hours at 90 °C. The solution was concentrated to remove the

methanol then extracted with CH_2Cl_2. The combined extracts were washed with a solution of sat. sodium potassium tartrate and dried over $MgSO_4$. The residue was purified *via* flash column (Ethyl acetate / Hexane, 5:95) to give **47** (775mg, 2.4mmol, 79%).

Preparation of **48**

To a solution of **47** (30 mg, 0.09mmol) in ethyl acetate / MeOH (2.0mL / 1.0mL, 2:1) was added Pd/C (16mg) and stirred under hydrogen atmosphere for 6 hours. The mixture was filtered through a celite pad and concentrated to give crude **48** (29mg).

Preparation of **49**

To a solution of **48** (29mg, 0.12mmol) in CH_2Cl_2 (2.0mL) at 0 °C was added Dess-Martin periodinane (78 mg, 0.18 mmol) and stirred for 3 hours. A solution of sat. $Na_2S_2O_3$ was added to the mixture and stirred for 10 minutes then $NaHCO_3$ was added. After 40 minutes of stirring, the organic layer was extracted with ethyl acetate then CH_2Cl_2 and dried over $MgSO_4$ to afford compound 14 (20mg, 0.09mmol, 75%).

Preparation of **50**

To a solution of **9** (63 mg, 0.20 mmol) in THF (3.0mL) at 0 °C was added *n*-BuLi (0.08mL, 0.20mmol) and stirred for 15 minutes. To this was added a solution of **49** (16 mg, 0.07mmol) in THF (3.0mL) followed by $Ti(O^iPr)_4$ (0.06mL, 0.20 mmol). The mixture was diluted with ethyl acetate after 4 hours of stirring and poured into H_2O. It was extracted with ethyl acetate then CH_2Cl_2, dried over $MgSO_4$ and the crude product purified by preparative TLC using 4:6 ethyl acetate-hexanes to provide **50** (29mg, 0.07 mmol, ~100%).

Preparation of **54**

To a solution of **53** (162mg, 0.50mmol) in THF (3.0mL) at 0 °C was added *n*-BuLi (0.20mL, 0.48mmol) and stirred for 15 minutes. To this was added a solution of **49** (20mg, 0.08mmol) in THF (3.0mL), followed by $Ti(O^iPr)_4$ (0.15mL, 0.50mmol) and stirred for 4 hours. The reaction mixture was washed with H_2O, dried over $MgSO_4$ and evaporated. The residue was purified via preparative TLC (Ethyl acetate, 100%) to afford compound **54** (23mg, 0.06mmol, 71%).

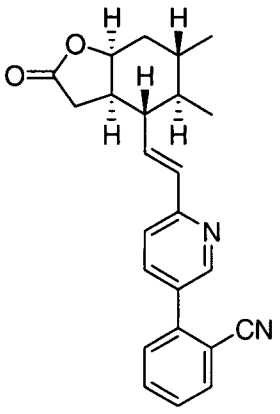
MS: m/z 406 [MH^+]

Preparation of **51**

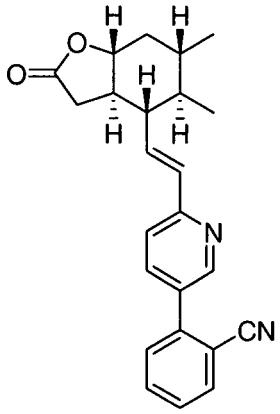
A mixture **50** (17mg, 0.04mmol), 2,5-difluorophenylboronic acid (30mg, 0.21mmol) and tetrakis(triphenyl phosphine)palladium (10mg) in toluene:H_2O:EtOH (2.0mL:1.0mL:0.5mL) was heated at reflux under N_2 atmosphere and stirred for 24 hours. After aqueous work-up, the crude material was purified *via* preparative TLC to give 13 mg of **51**.

MS: m/z 406 [MH^+].

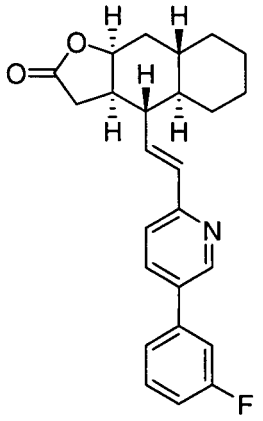
The compound **52** was prepared using a similar procedure.
MS: m/z 455 [MH^+]

Compound	Structure
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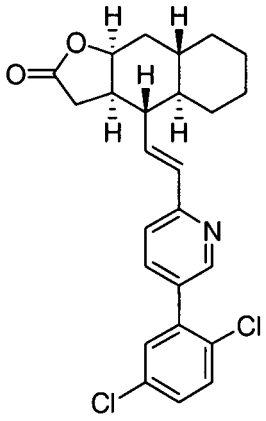
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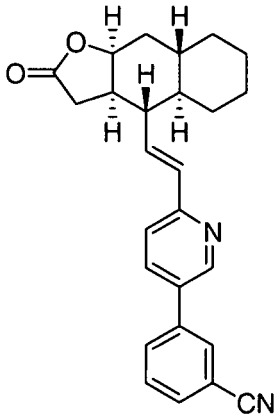
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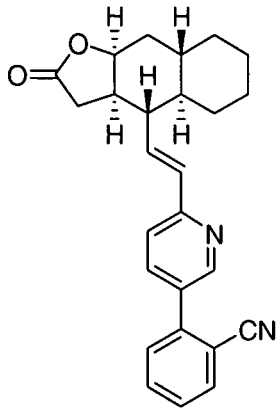
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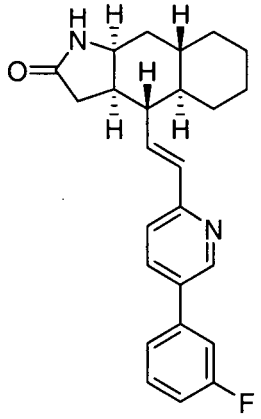
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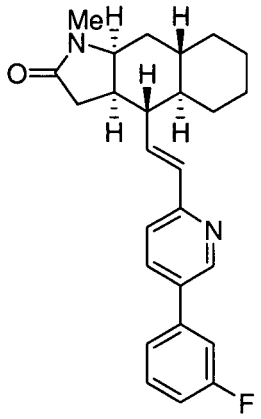
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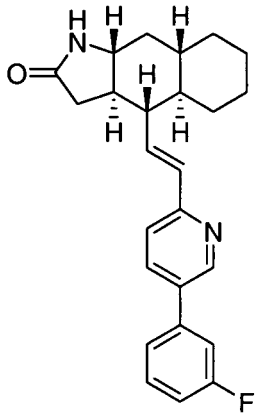
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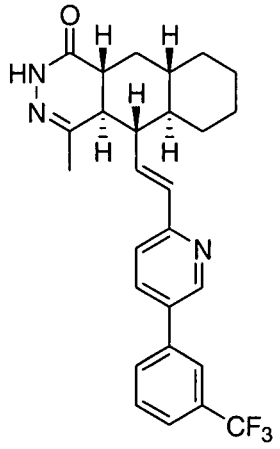
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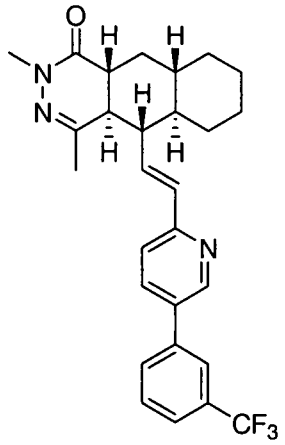
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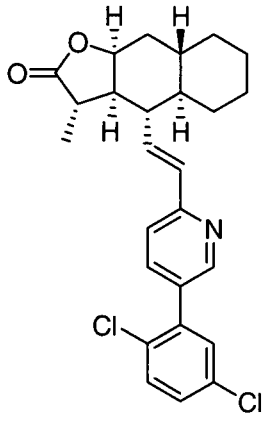
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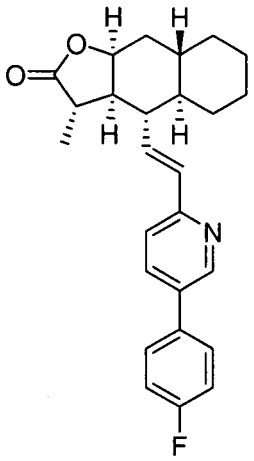
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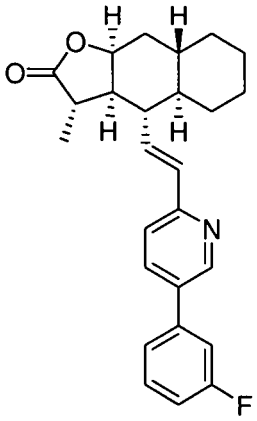
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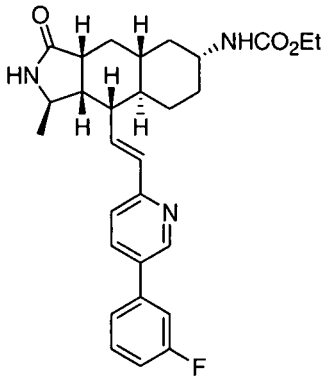
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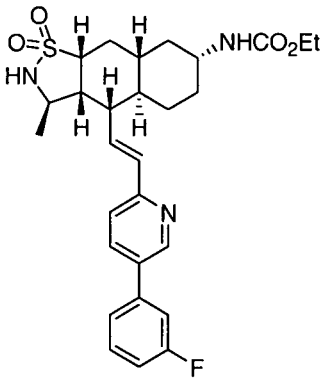


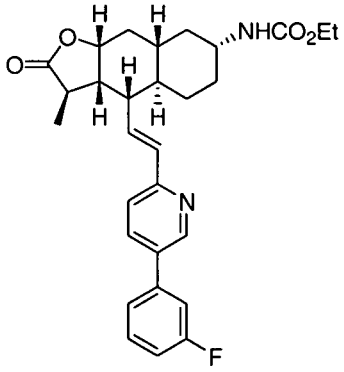
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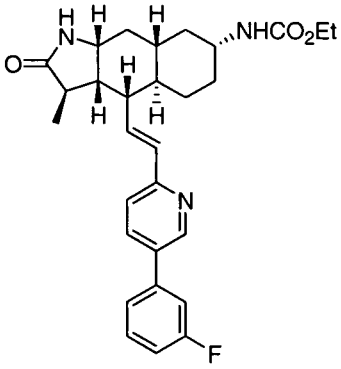


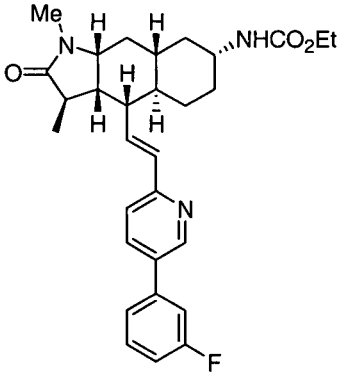
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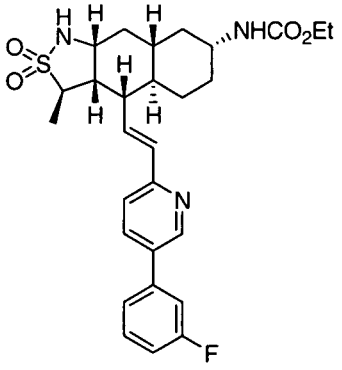


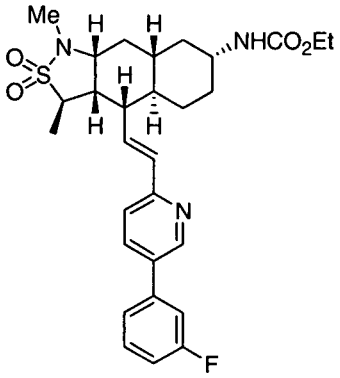


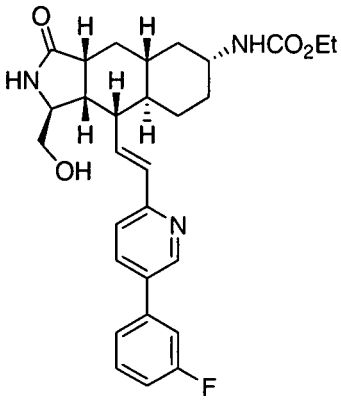


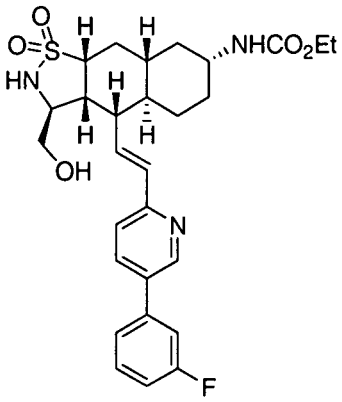


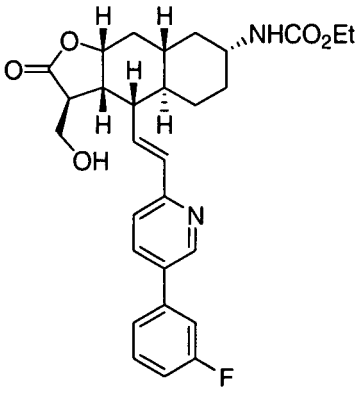


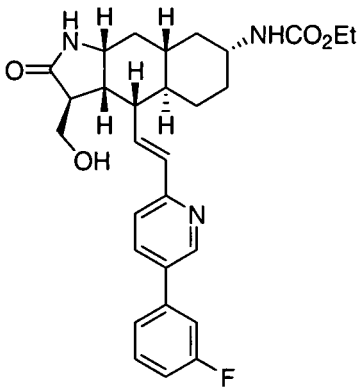


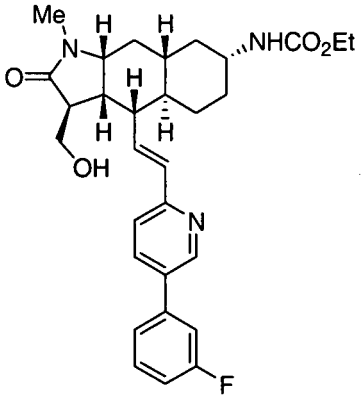


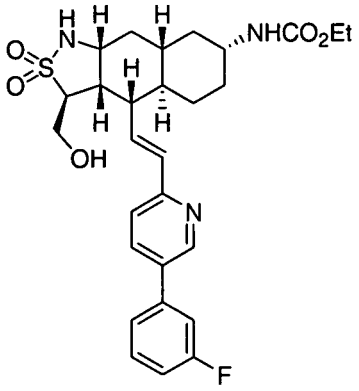


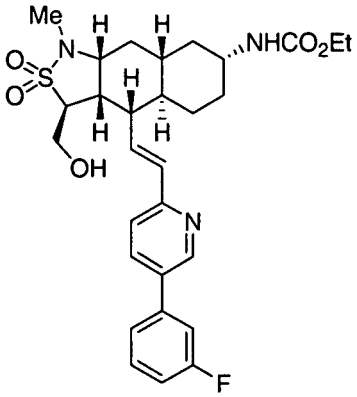


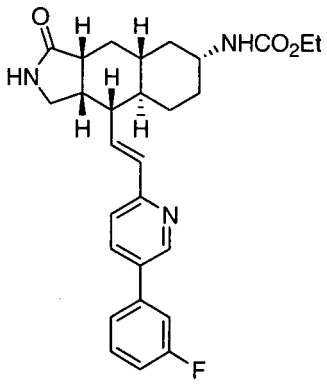


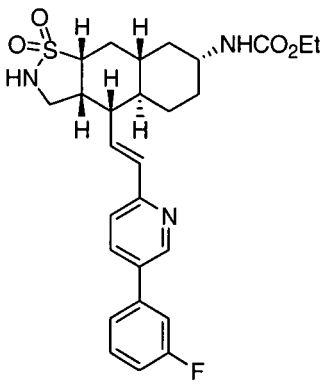


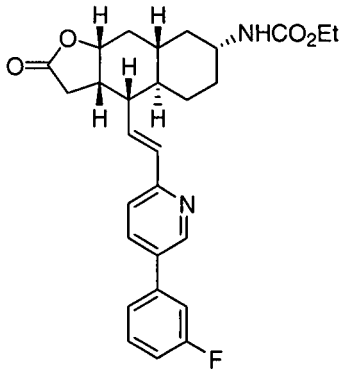


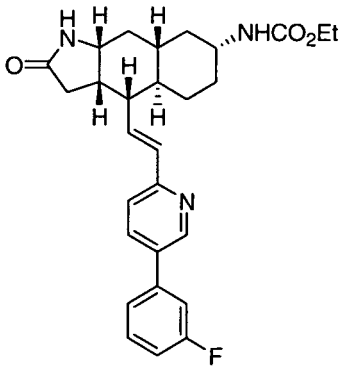


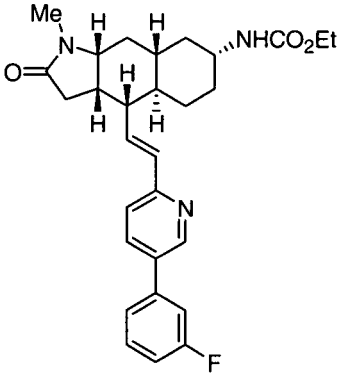


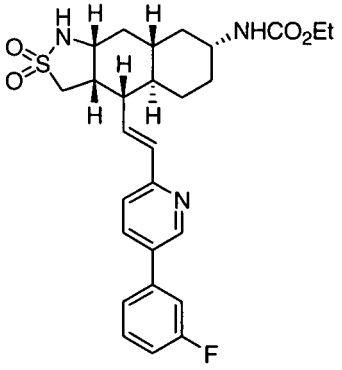


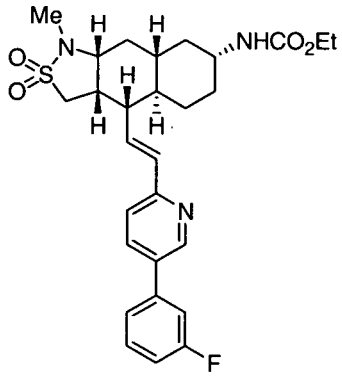


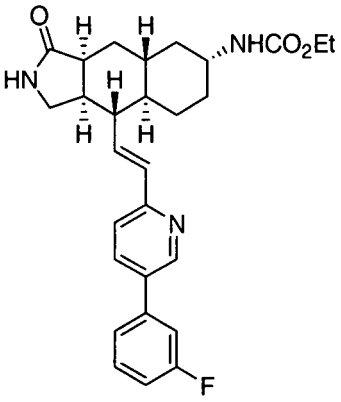


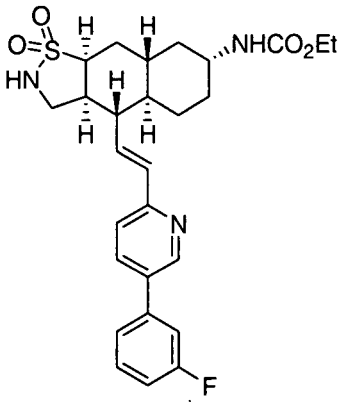


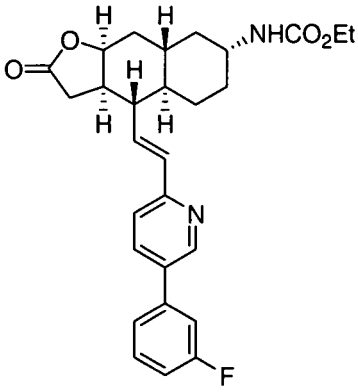


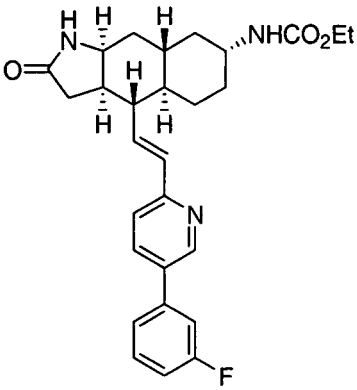


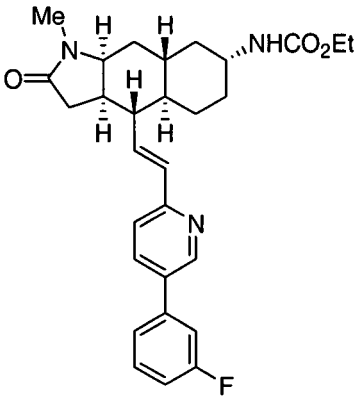


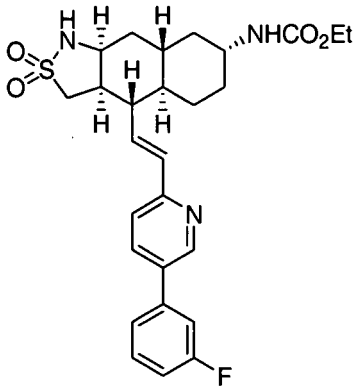


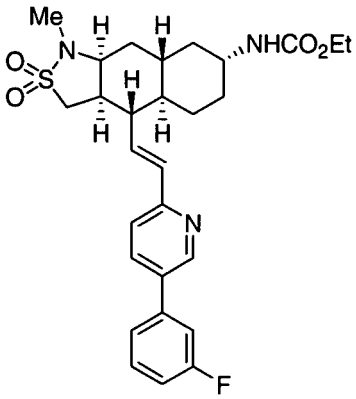


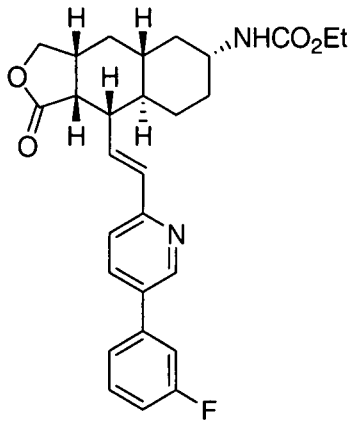


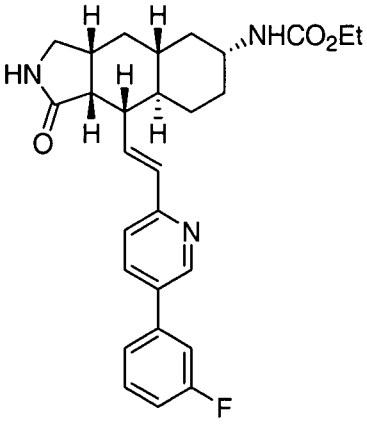


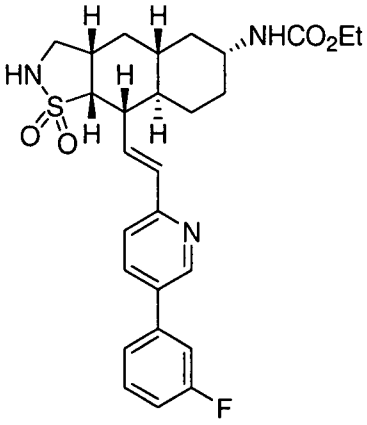


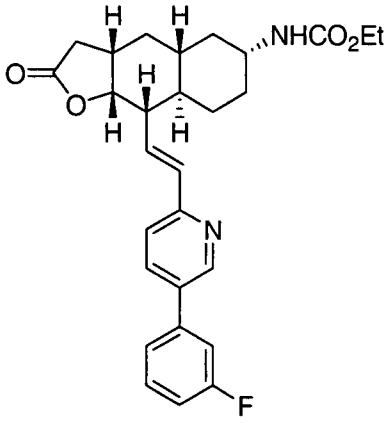


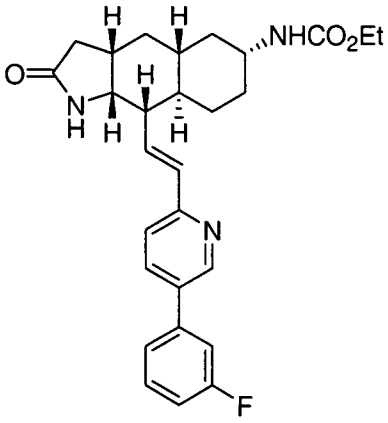


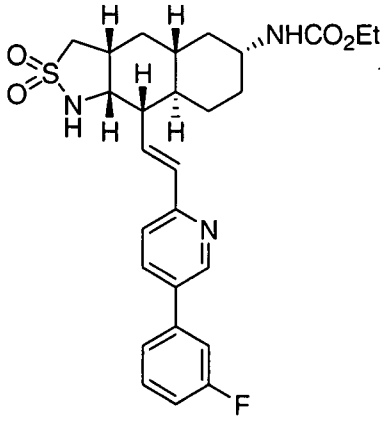


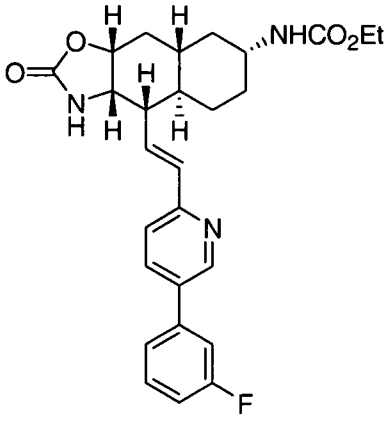


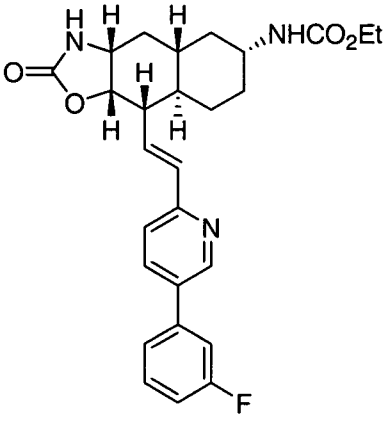


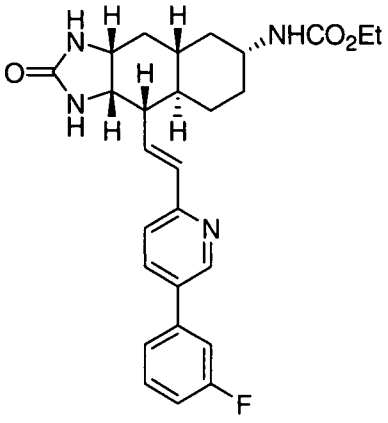




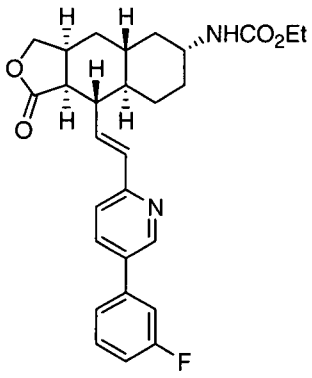


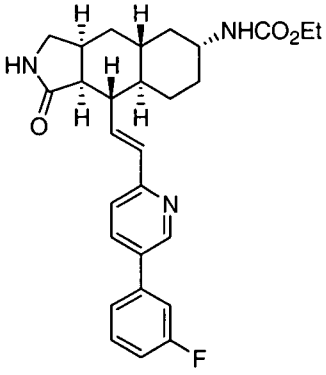


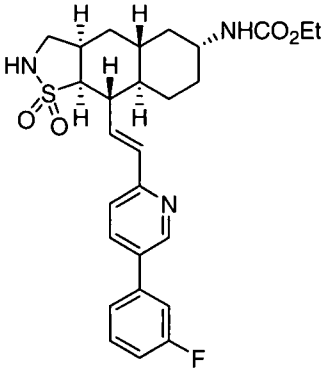


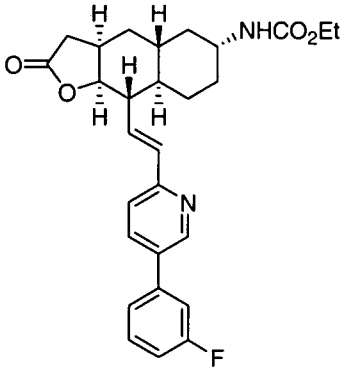


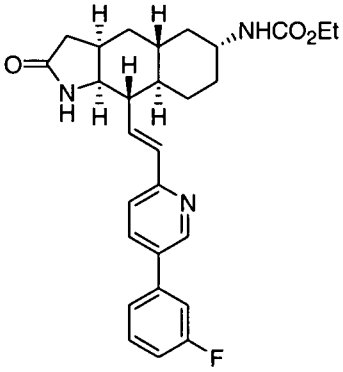
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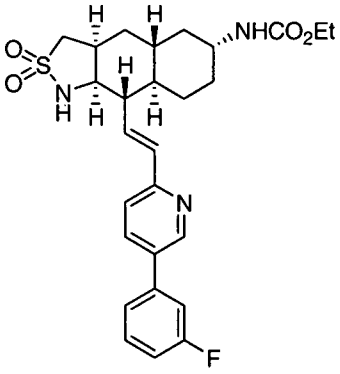


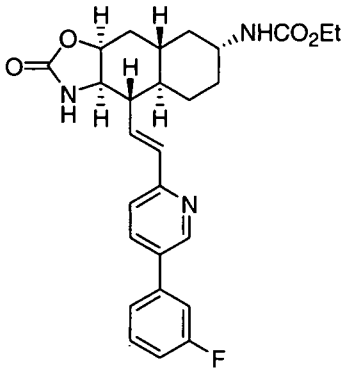


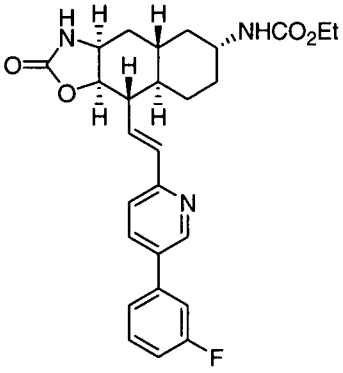


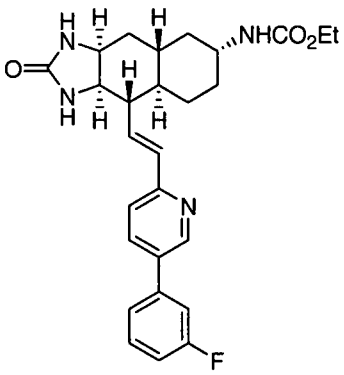




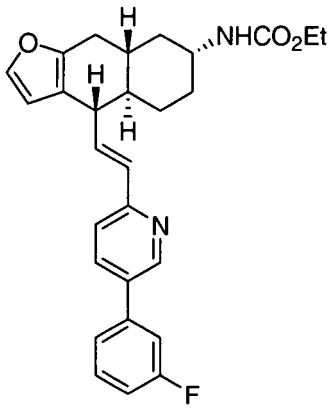
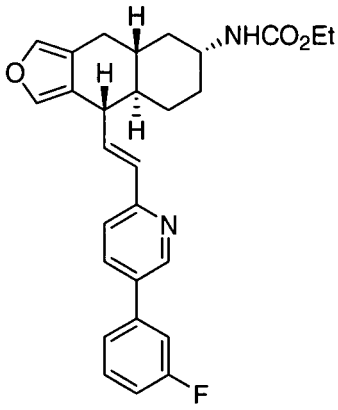
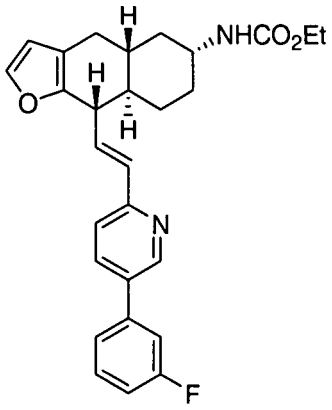
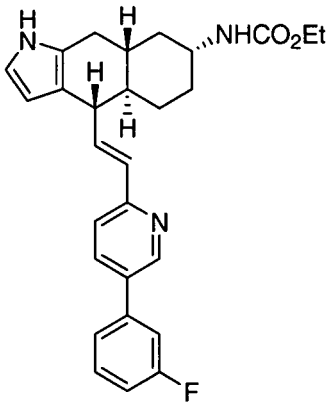
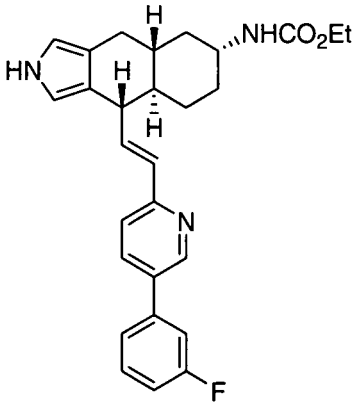
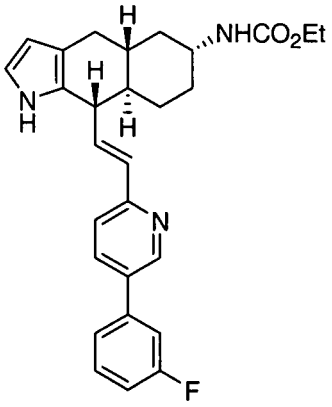
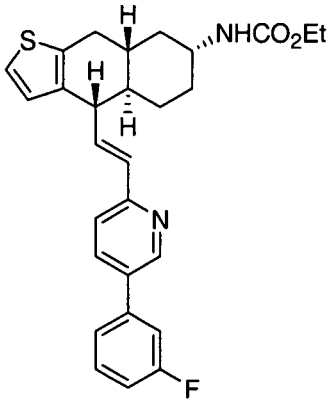
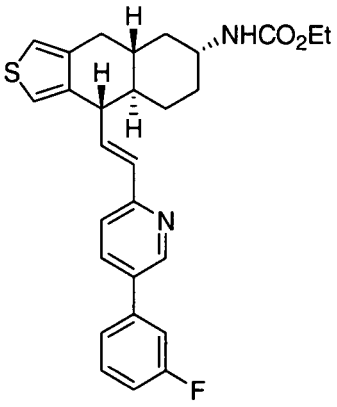
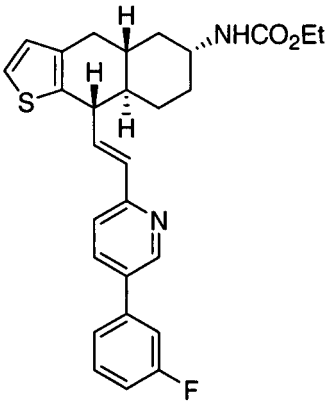


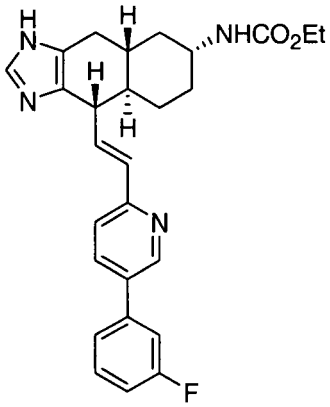


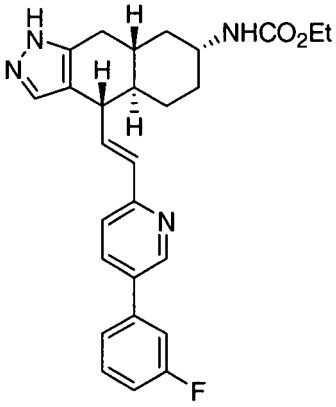


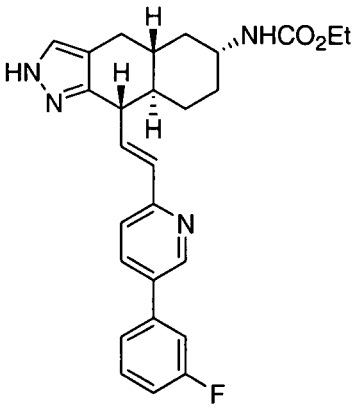


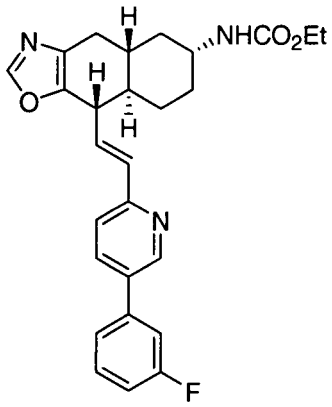
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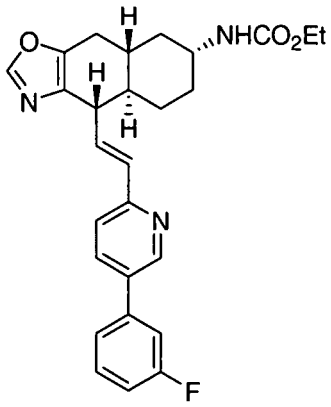










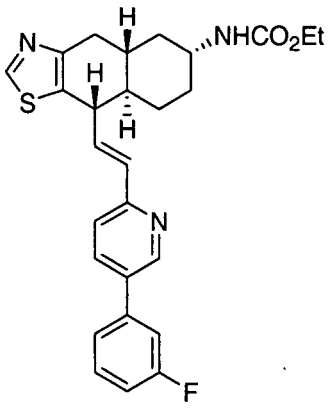


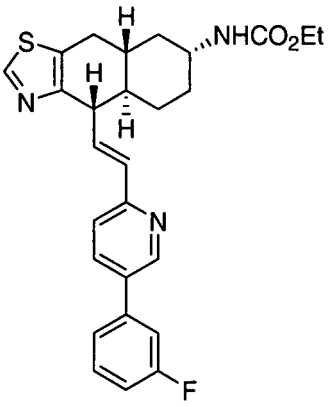




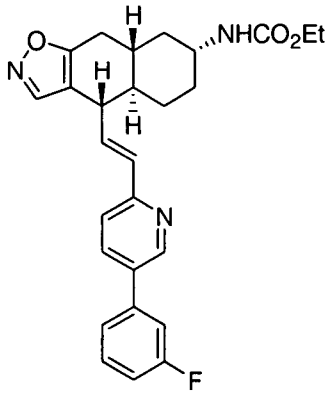


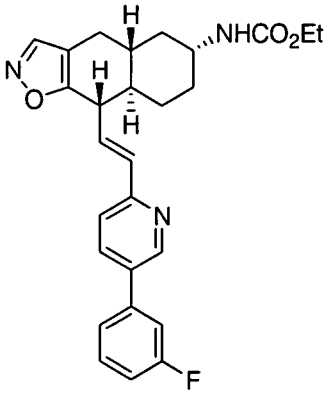


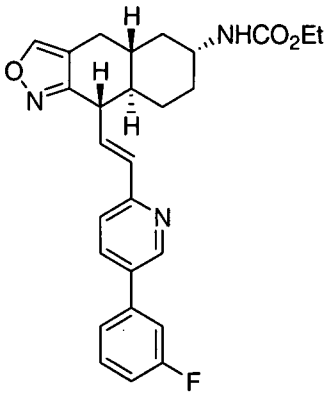


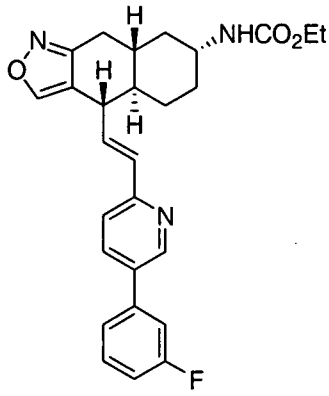


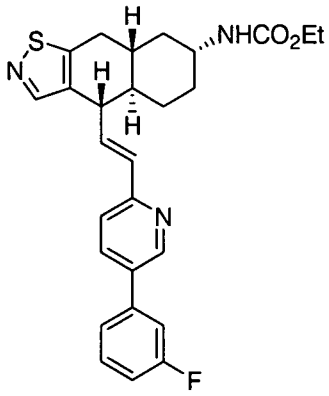
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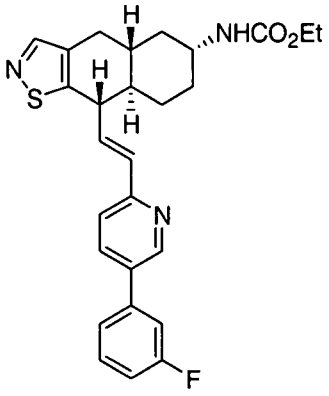


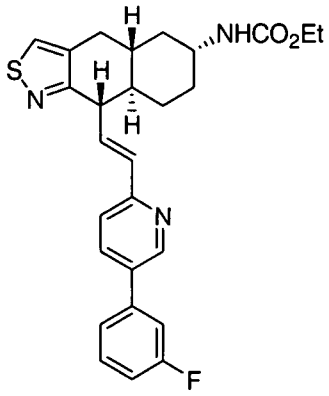


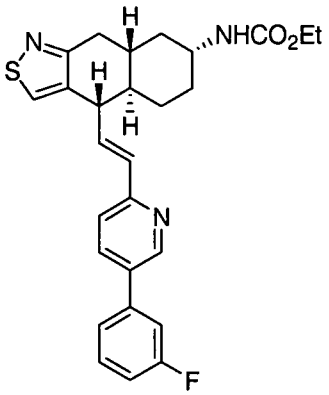






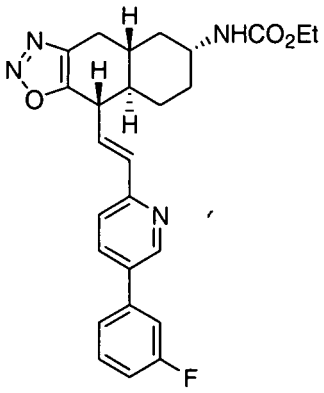


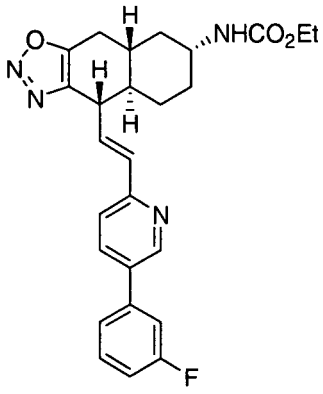


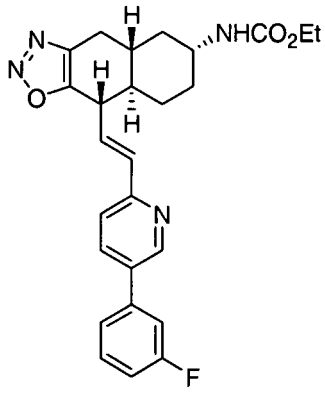


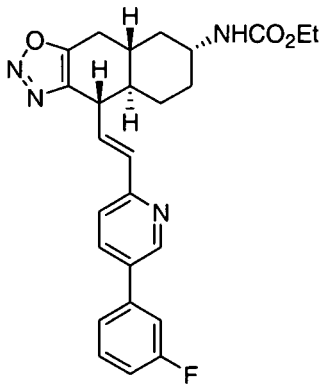
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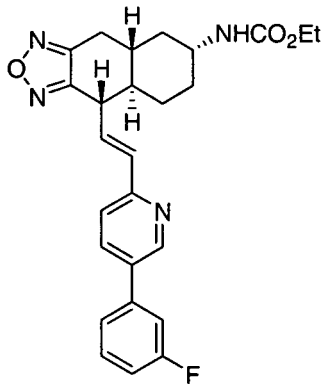
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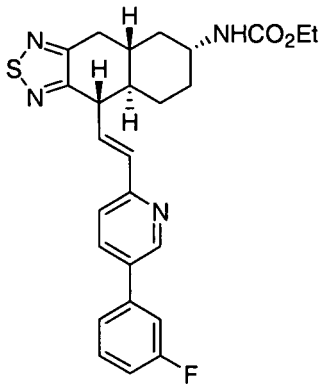


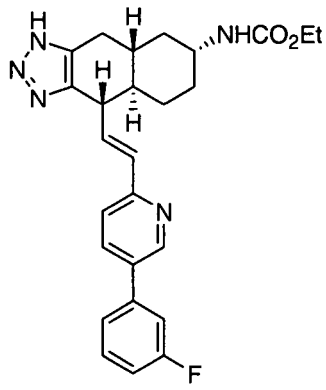


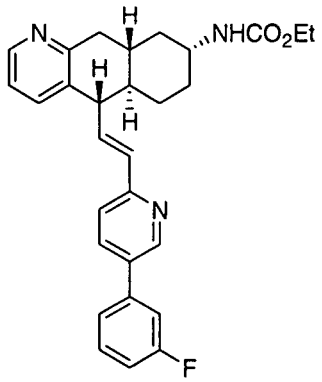


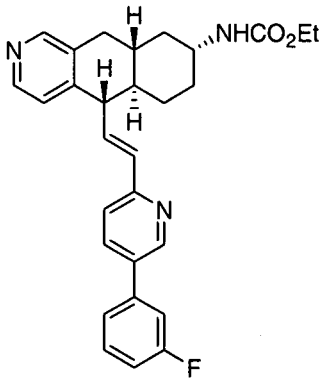


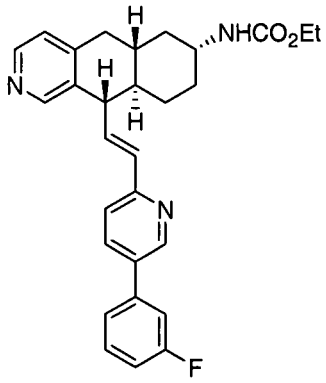


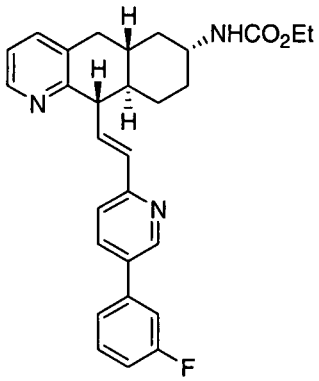


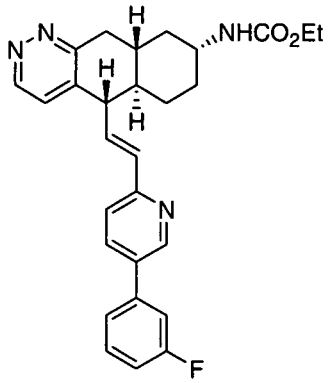


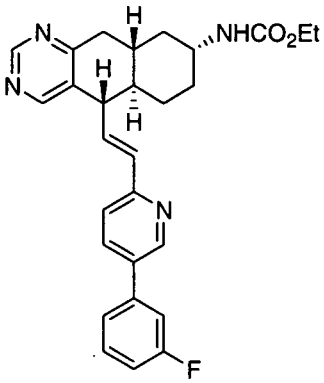


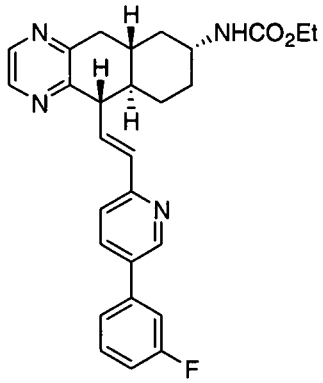


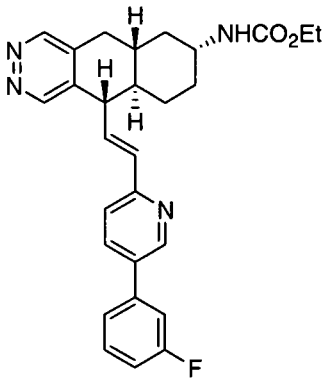


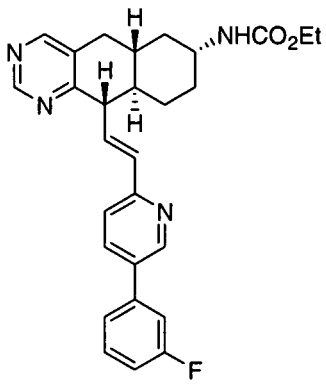


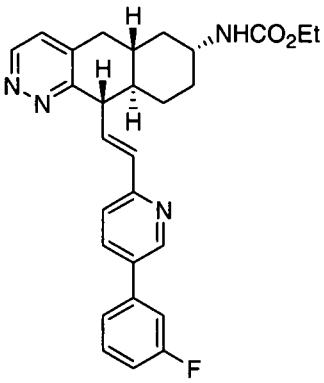


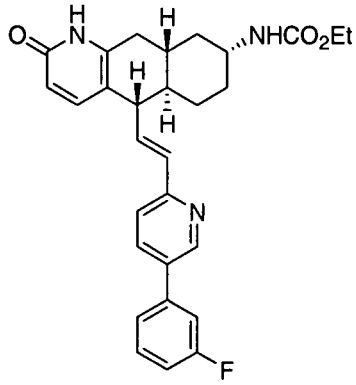


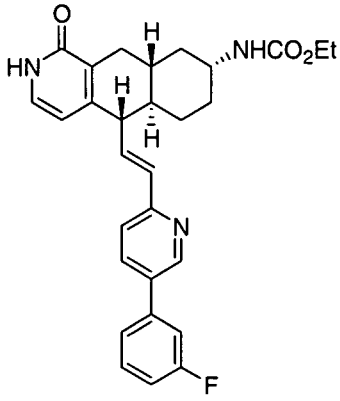


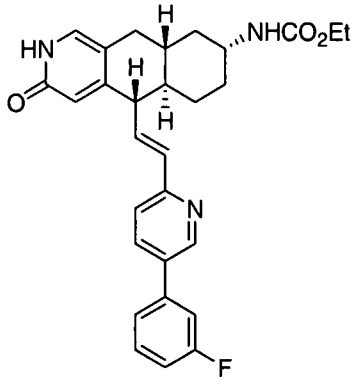


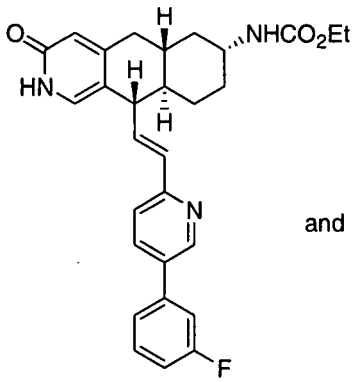




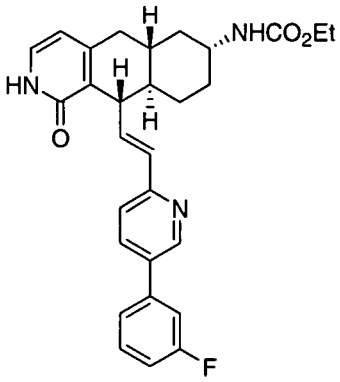






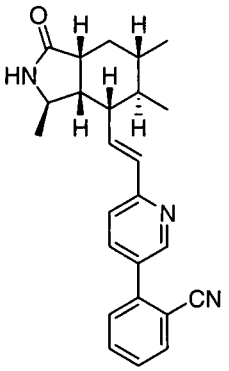


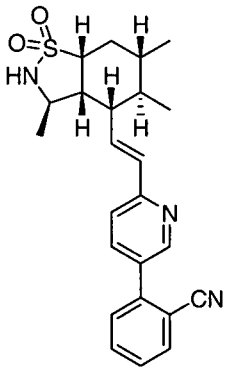
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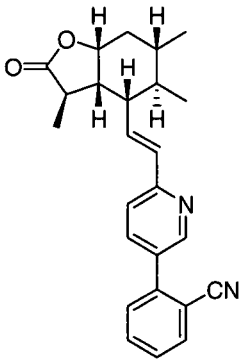


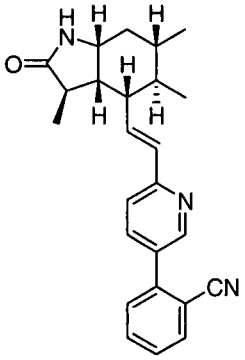
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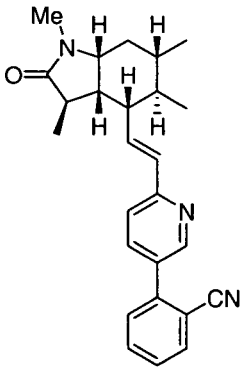
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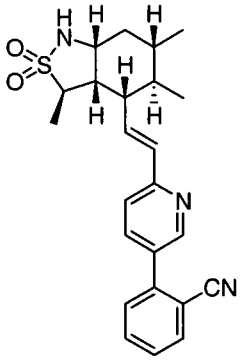


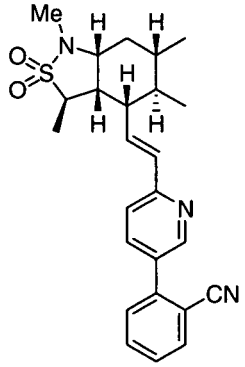


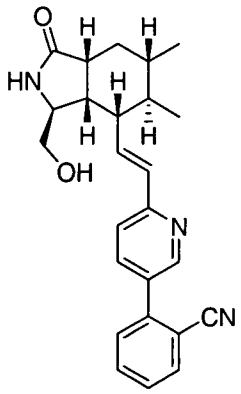


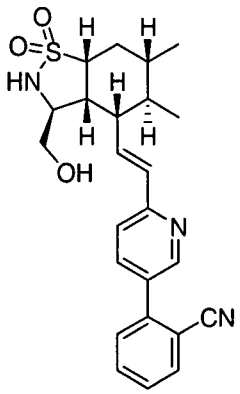


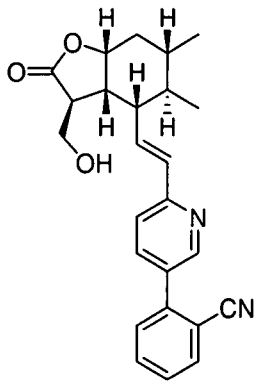


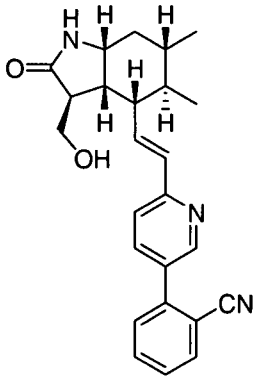


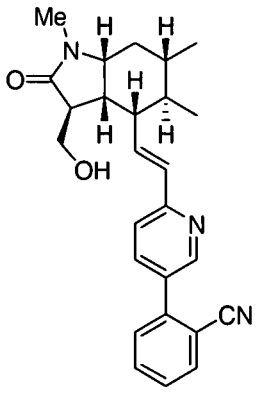


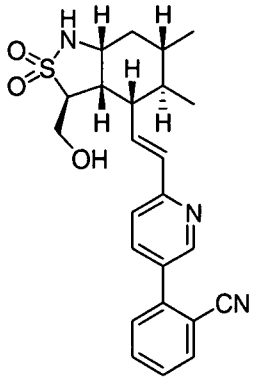


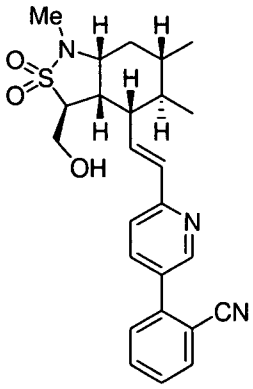


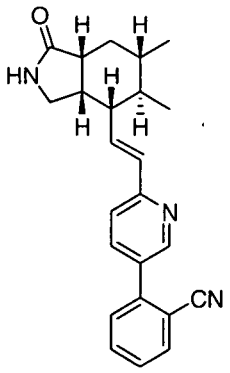


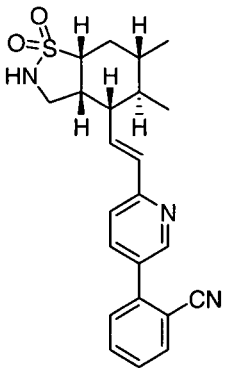


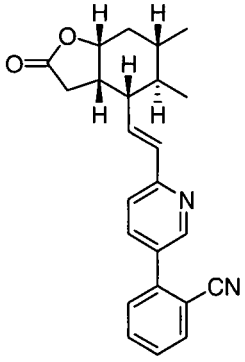


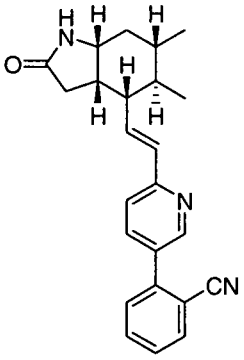


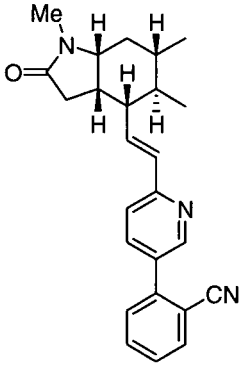


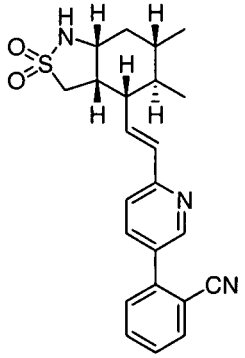


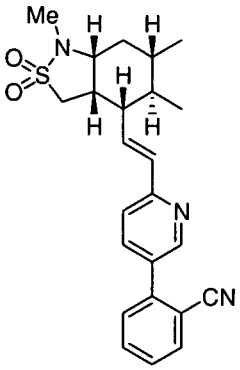


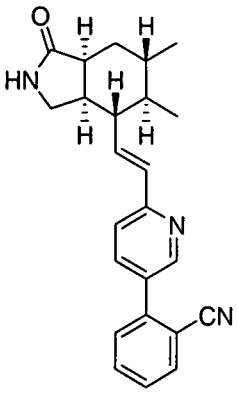


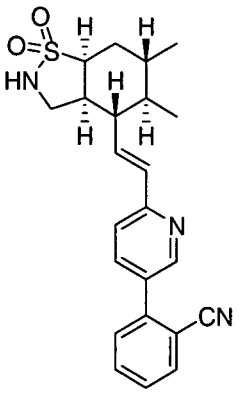


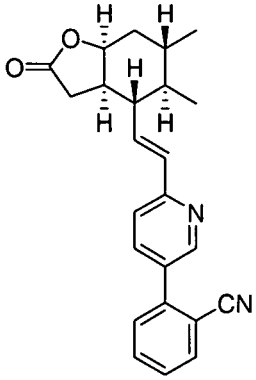


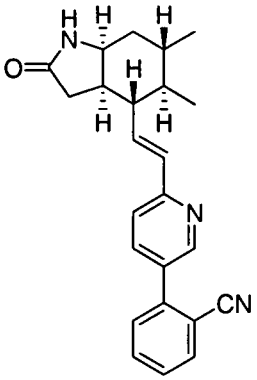


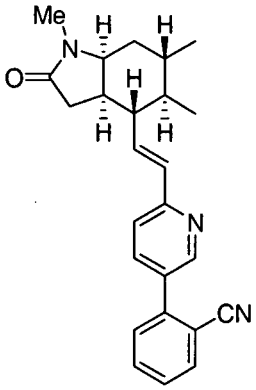


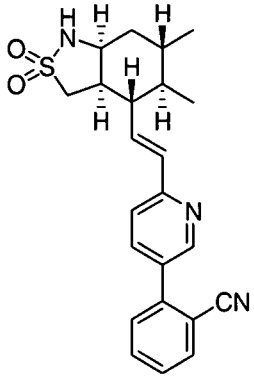


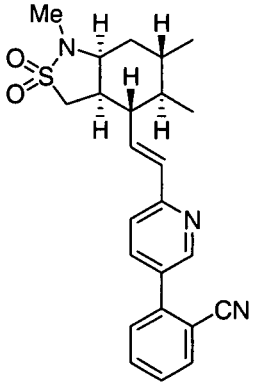


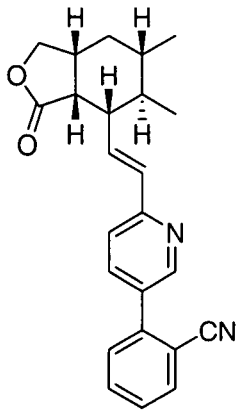


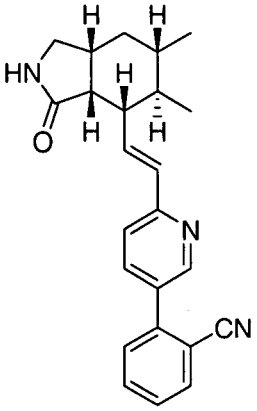


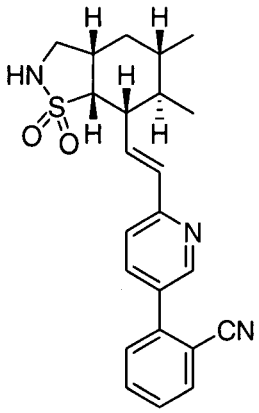


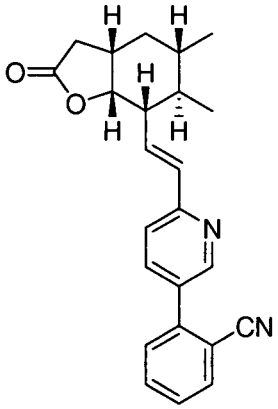


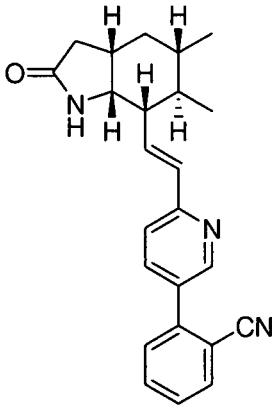


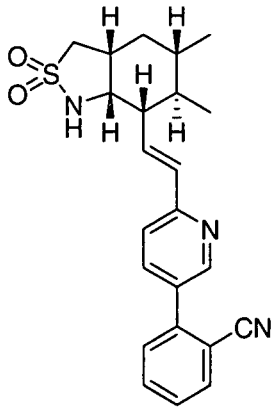


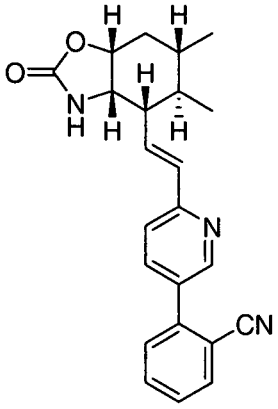


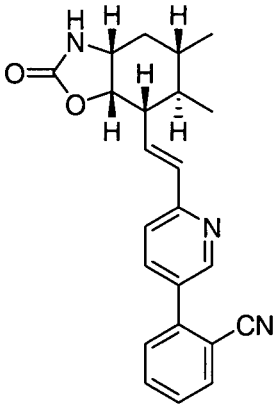


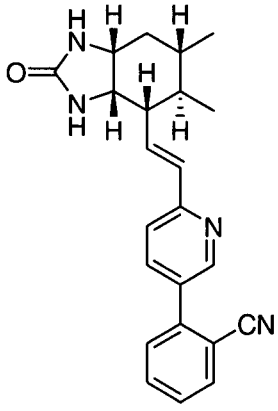


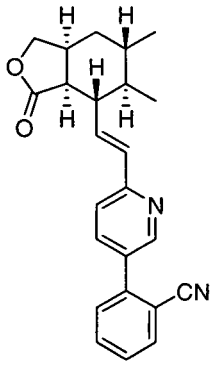
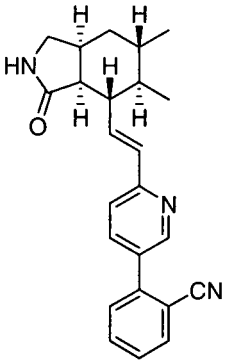
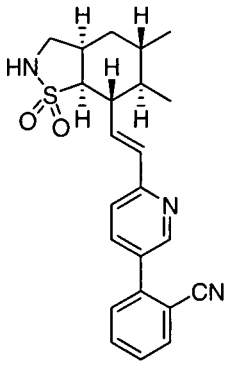
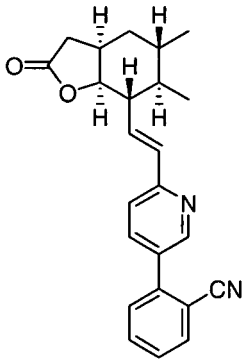
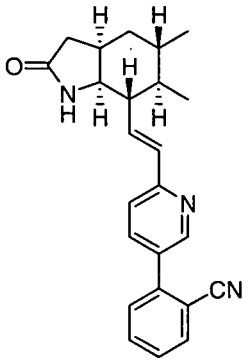
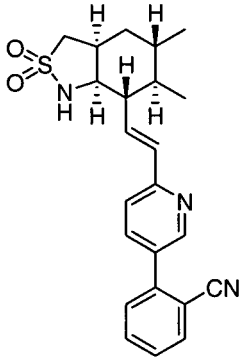
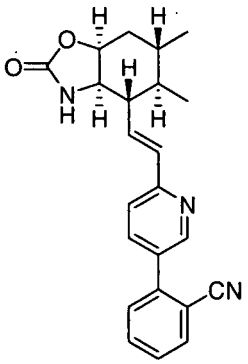
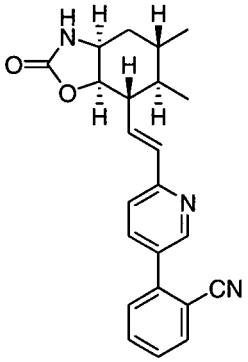
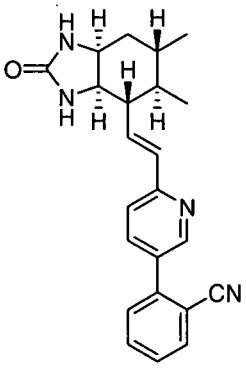




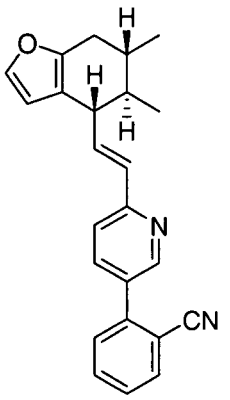
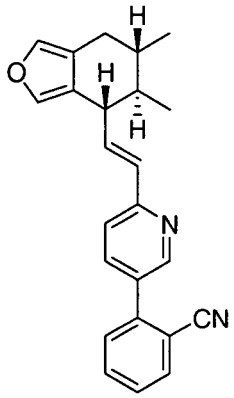
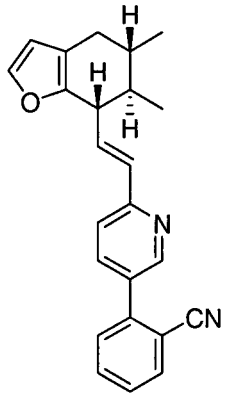
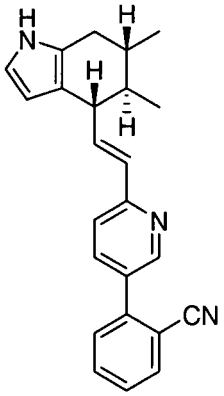
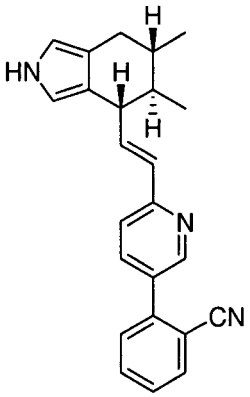
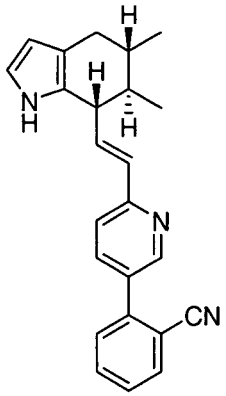
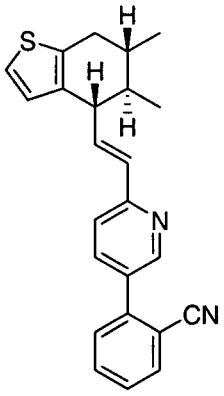
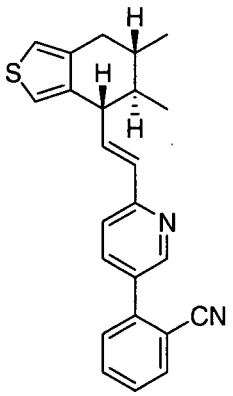
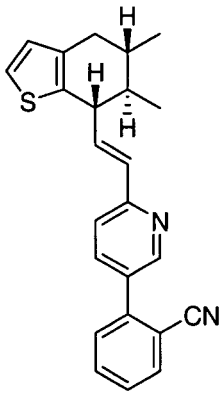


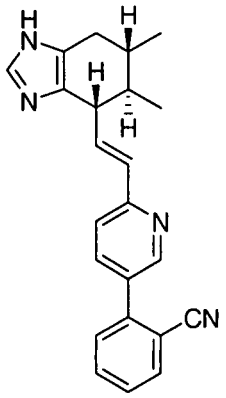


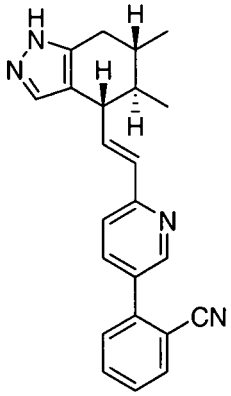


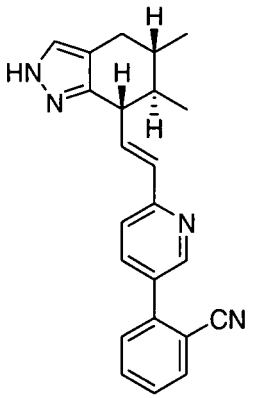










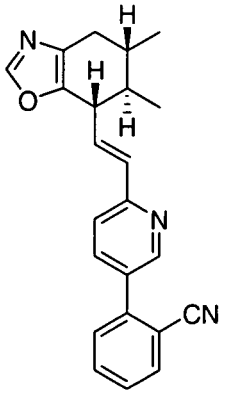
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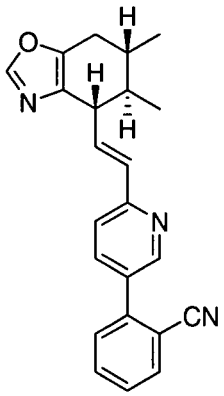










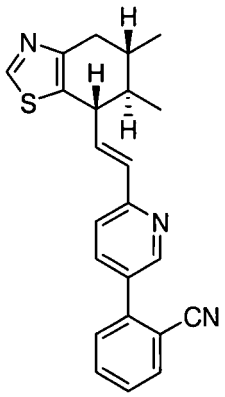


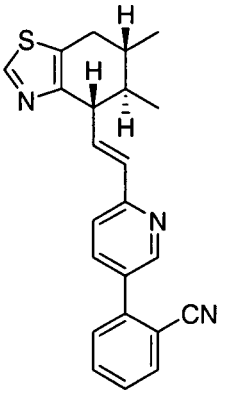




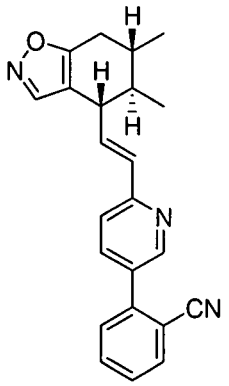


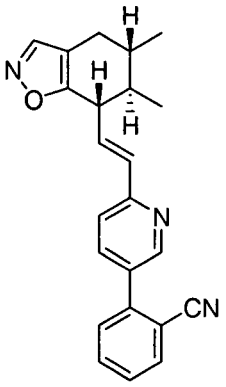


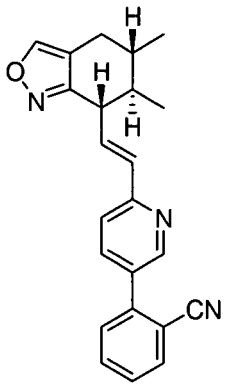


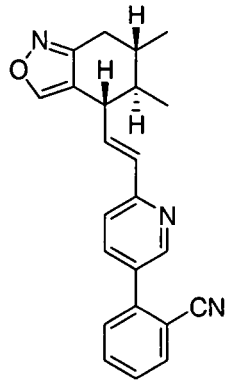


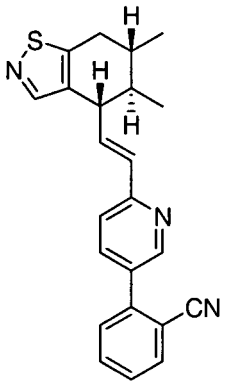
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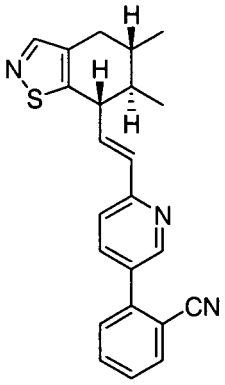


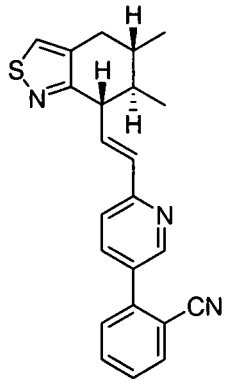


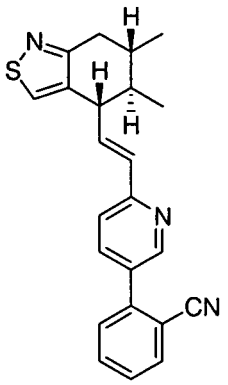






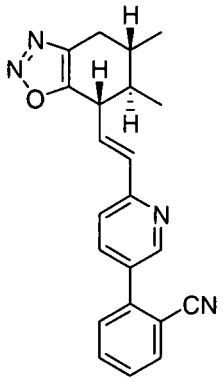


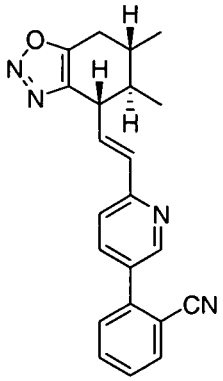


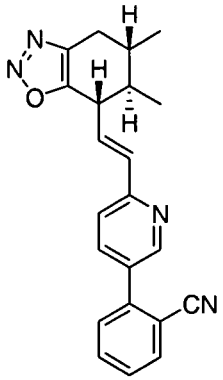


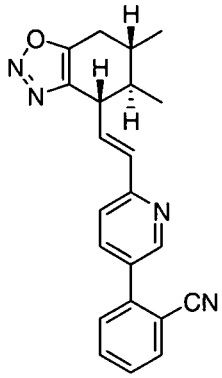
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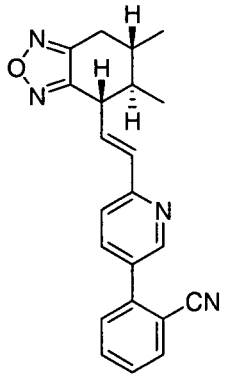
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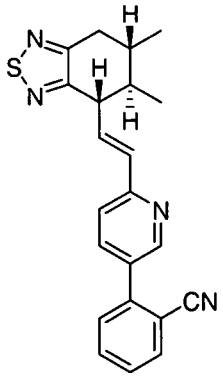


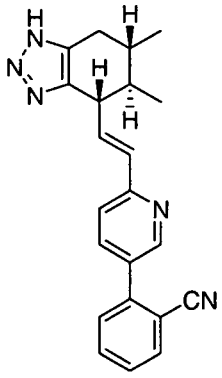




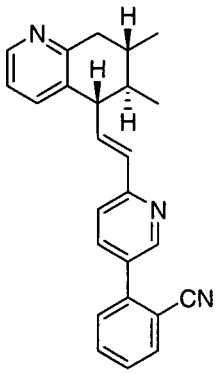


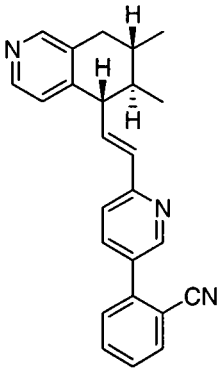


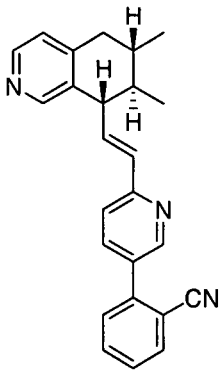


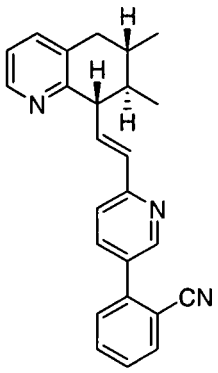


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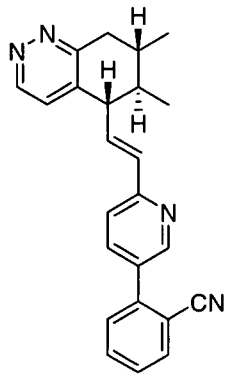


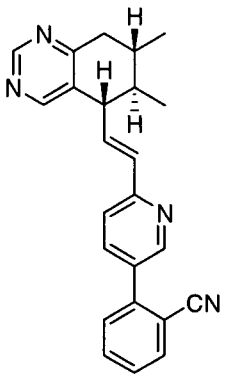


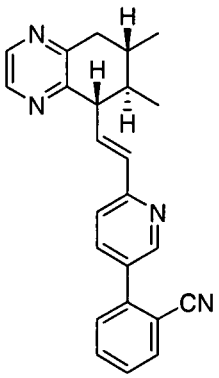


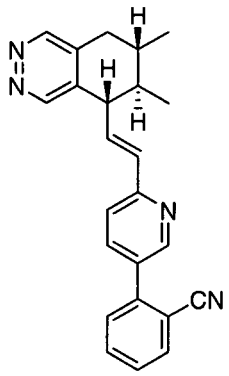


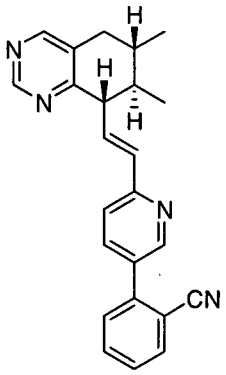
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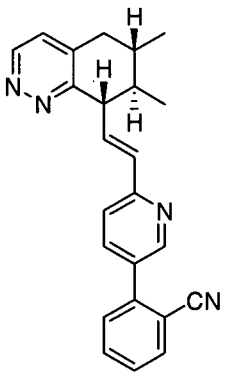


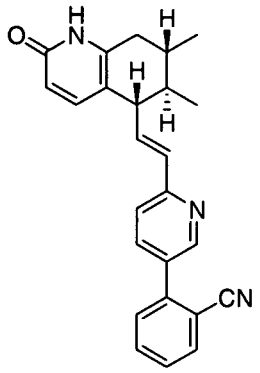


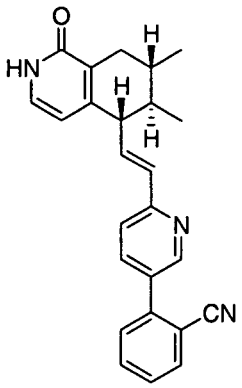


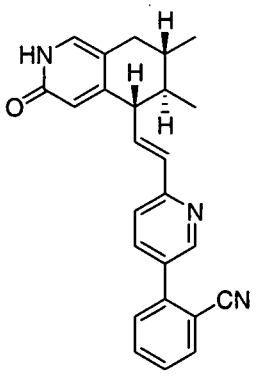


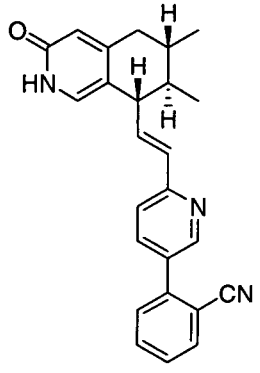




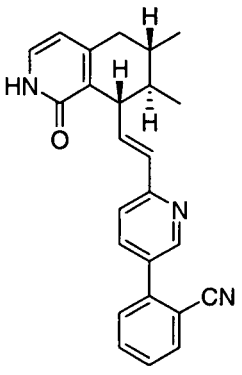








and



Further embodiments of the invention encompass the administration of compounds of Formula I along with at least one additional agent. The contemplated additional agent is one that differs in either atomic make up or arrangement from the compounds of Formula I. Additional agents that can be used in combination with the novel compounds of this invention include drugs which have anti-thrombotic, anti-platelet aggregation, antiatherosclerotic, antirestenotic and/or anti-coagulant activity. Such drugs are useful in treating thrombosis-related diseases including thrombosis, atherosclerosis, restenosis, hypertension, angina pectoris, angiogenesis related disorders, arrhythmia, a cardiovascular or circulatory disease or condition, heart failure, myocardial infarction, glomerulonephritis, thrombotic stroke, thromboembolytic stroke, peripheral vascular diseases, cerebral ischemia, rheumatoid arthritis, rheumatism, astrogliosis, a fibrotic disorder of the liver, kidney, lung or intestinal tract, systemic lupus erythematosus, multiple sclerosis, osteoporosis, glomerulonephritis, renal disease, acute renal failure, chronic renal failure, renal vascular homeostasis, renal ischemia, bladder inflammation, diabetes, diabetic neuropathy, cerebral stroke, cerebral ischemia, nephritis, cancer, melanoma, renal cell carcinoma, neuropathy and/or malignant tumors, neurodegenerative and/or neurotoxic diseases, conditions, or injuries, inflammation, asthma, glaucoma, macular degeneration, psoriasis, endothelial dysfunction disorders of the liver, kidney or lung inflammatory disorders of the lungs and gastrointestinal tract, respiratory tract disease or condition, radiation fibrosis, endothelial dysfunction, periodontal diseases or wounds or a spinal cord injury, or a symptom or result thereof, as well as other disorders in which thrombin and its receptor play a pathological role.

Suitable cardiovascular agents are selected from the group consisting of thromboxane A2 biosynthesis inhibitors; thromboxane antagonists; adenosine diphosphate inhibitors; cyclooxygenase inhibitors; angiotensin antagonists; endothelin antagonists; phosphodiesterase inhibitors; angiotensin converting enzyme inhibitors; neutral endopeptidase inhibitors; anticoagulants; diuretics; platelet aggregation inhibitors; and GP IIb/IIIa antagonists.

Preferred types of drugs for use in combination with the novel compounds of this invention are thromboxane A2 biosynthesis inhibitors, GP IIb/IIIa antagonists, thromboxane antagonists, adenosine diphosphate inhibitors, cyclooxygenase inhibitors, angiotensin antagonists, endothelin antagonists, angiotensin converting

enzyme inhibitors, neutral endopeptidase inhibitors, anticoagulants, diuretics, and platelet aggregation inhibitors.

In particular, suitable cardiovascular agents are selected from the group consisting of aspirin, seratrodast, picotamide and ramatroban, clopidogrel, meloxicam, rofecoxib, celecoxib, valsartan, telmisartan, candesartran, irbesartran, losartan, eprosartan, tezosentan, milrinoone, enoximone, captopril, enalapril, enaliprilat, spirapril, quinapril, perindopril, ramipril, fosinopril, trandolapril, lisinopril, moexipril, benazapril, candoxatril, ecadotril, ximelagatran, fondaparin, enoxaparin, chlorothiazide, hydrochlorothiazide, ethacrynic acid, furosemide, amiloride, abciximab, eptifibatide, prasugrel and fragmin.

Especially preferred for use in the combinations are aspirin, cangrelor, clopidogrel bisulfate, prasugrel and fragmin.

When the invention comprises a combination of a compound of Formula I and another agent, the two active components may be co-administered simultaneously or sequentially, or a single pharmaceutical composition comprising a compound of Formula I and another agent in a pharmaceutically acceptable carrier can be administered. The components of the combination can be administered individually or together in any conventional dosage form such as capsule, tablet, powder, cachet, suspension, solution, suppository, nasal spray, etc. The dosage of the cardiovascular agent can be determined from published material, and may range from 1 to 1000 mg per dose.

In this specification, the term "at least one compound of Formula I" means that one to three different compounds of Formula I may be used in a pharmaceutical composition or method of treatment. Preferably one compound of Formula I is used. Similarly, the term "one or more additional cardiovascular agents" means that one to three additional drugs may be administered in combination with a compound of Formula I; preferably, one additional compound is administered in combination with a compound of Formula I. The additional agents can be administered sequentially or simultaneously with reference to the compound of Formula I.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art,

e.g. magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), *The Science and Practice of Pharmacy*, 20th Edition, (2000), Lippincott Williams & Wilkins, Baltimore, MD.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 1 mg to about 150 mg, preferably from about 1 mg to about 75 mg, more preferably from about 1 mg to about 50 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For

convenience, the total daily dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 1 mg/day to about 300 mg/day, preferably 1 mg/day to 75 mg/day, in two to four divided doses.

When separate compounds of Formula I and the other agents are to be administered as separate compositions, they can be provided in a kit comprising in a single package, one container comprising a compound of Formula I in a pharmaceutically acceptable carrier, and a separate container comprising another cardiovascular agent in a pharmaceutically acceptable carrier, with the compound of Formula I and the other agent being present in amounts such that the combination is therapeutically effective. A kit is advantageous for administering a combination when, for example, the components must be administered at different time intervals or when they are in different dosage forms.

The activity of the compounds of formula I can be determined by the following procedures.

<u>In Vitro Testing Procedure for Thrombin Receptor Antagonists:</u>

<u>Preparation of [^{3}H]haTRAP</u>

A(pF-F)R(ChA)(hR)(I_2-Y)-NH_2 (1.03 mg) and 10% Pd/C (5.07 mg) were suspended in DMF (250 μl) and diisopropylethylamine (10 μl). The vessel was attached to the tritium line, frozen in liquid nitrogen and evacuated. Tritium gas (342 mCi) was then added to the flask, which was stirred at room temperature for 2 hours. At the completion of the reaction, the excess tritium was removed and the reacted peptide solution was diluted with DMF (0.5 ml) and filtered to remove the catalyst. The collected DMF solution of the crude peptide was diluted with water and freeze dried to remove the labile tritium. The solid peptide was redissolved in water and the freeze drying process repeated. The tritiated peptide ([^{3}H]haTRAP) was dissolved in 0.5 ml of 0.1% aqueous TFA and purified by HPLC using the following conditions: column, Vydac™ C18, 25 cm x 9.4 mm I.D.; mobile phase, (A) 0.1% TFA in water, (B) 0.1%

TFA in CH_3CN; gradient, (A/B) from 100/0 to 40/60 over 30 min; flow rate, 5 ml /min; detection, UV at 215 nm. The radiochemical purity of [^{3}H]haTRAP was 99% as analyzed by HPLC. A batch of 14.9 mCi at a specific activity of 18.4 Ci/mmol was obtained.

Preparation of platelet membranes

Platelet membranes were prepared using a modification of the method of Natarajan *et al.* (Natarajan *et al*, Int. J. Peptide Protein Res. 45:145-151 (1995)) from 20 units of platelet concentrates obtained from the North Jersey Blood Center (East Orange, NJ) within 48 hours of collection. All steps were carried out at 4° C under approved biohazard safety conditions. Platelets were centrifuged at 100 x g for 20 minutes at 4° C to remove red cells. The supernatants were decanted and centrifuged at 3000 x g for 15 minutes to pellet platelets. Platelets were re-suspended in 10 mM Tris-HCl, pH 7.5, 150 mM NaCl, 5 mM EDTA, to a total volume of 200 ml and centrifuged at 4400 x g for 10 minutes. This step was repeated two additional times. Platelets were re-suspended in 5 mM Tris-HCl, pH 7.5, 5 mM EDTA to a final volume of approximately 30 ml and were homogenized with 20 strokes in a Dounce™ homogenizer. Membranes were pelleted at 41,000 x g, re-suspended in 40-50 ml 20 mM Tris-HCl, pH 7.5, 1 mM EDTA, 0.1 mM dithiothreitol, and 10 ml aliquots were frozen in liquid N_2 and stored at -80° C. To complete membrane preparation, aliquots were thawed, pooled, and homogenized with 5 strokes of a Dounce homogenizer. Membranes were pelleted and washed 3 times in 10 mM triethanolamine-HCl, pH 7.4, 5 mM EDTA, and re-suspended in 20-25 ml 50 mM Tris-HCl, pH 7.5, 10 mM $MgCl_2$, 1 mM EGTA, and 1% DMSO. Aliquots of membranes were frozen in liquid N_2 and stored at -80° C. Membranes were stable for at least 3 months. 20 units of platelet concentrates typically yielded 250 mg of membrane protein. Protein concentration was determined by a Lowry assay (Lowry *et al.*, J. Biol. Chem., 193:265-275 (1951)).

High Throughput Thrombin Receptor Radioligand Binding Assay

Thrombin receptor antagonists were screened using a modification of the thrombin receptor radioligand binding assay of Ahn *et al.* (Ahn *et al.*, Mol. Pharmacol., 51:350-356 (1997)). The assay was performed in 96 well Nunc plates (Cat. No. 269620) at a final assay volume of 200 µl. Platelet membranes and [^{3}H]haTRAP were diluted to 0.4 mg/ml and 22.2 nM, respectively, in binding buffer (50 mM Tris-HCl, pH

7.5, 10 mM $MgCl_2$, 1 mM EGTA, 0.1% BSA). Stock solutions (10 mM in 100% DMSO) of test compounds were further diluted in 100% DMSO. Unless otherwise indicated, 10 μl of diluted compound solutions and 90 μl of radioligand (a final concentration of 10 nM in 5% DMSO) were added to each well, and the reaction was started by the addition of 100 μl of membranes (40 μg protein/well). The binding was not significantly inhibited by 5% DMSO. Compounds were tested at three concentrations (0.1, 1 and 10 μM). The plates were covered and vortex-mixed gently on a Lab-Line™ Titer Plate Shaker for 1 hour at room temperature. Packard UniFilter™ GF/C filter plates were soaked for at least 1 hour in 0.1% polyethyleneimine. The incubated membranes were harvested using a Packard FilterMate™ Universal Harvester and were rapidly washed four times with 300 μl ice cold 50 mM Tris-HCl, pH 7.5, 10 mM $MgCl_2$, 1 mM EGTA. MicroScint™ 20 scintillation cocktail (25 μl) was added to each well, and the plates were counted in a Packard TopCount™ Microplate Scintillation Counter. The specific binding was defined as the total binding minus the nonspecific binding observed in the presence of excess (50 μM) unlabeled haTRAP. The % inhibition by a compound of [^{3}H]haTRAP binding to thrombin receptors was calculated from the following relationship:

$$\% \text{ Inhibition} = \frac{\text{Total binding-Binding in the presence of a test compound}}{\text{Total binding-Nonspecific binding}} \times 100$$

Materials

A(pF-F)R(ChA)(hR)Y-NH_2 and A(pF-F)R(ChA)(hR)(I_2-Y)-NH_2, were custom synthesized by AnaSpec Inc. (San Jose, CA). The purity of these peptides was >95%. Tritium gas (97%) was purchased from EG&G Mound, Miamisburg, Ohio. The gas was subsequently loaded and stored on an IN/US Systems Inc. Trisorber. MicroScint™ 20 scintillation cocktail was obtained from Packard Instrument Co.

Cannabinoid CB_2 Receptor Binding Assay

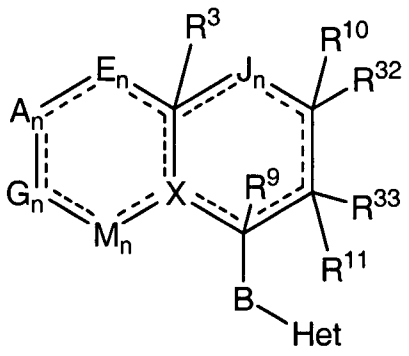
Binding to the human cannabinoid CB_2 receptor was carried out using the procedure of Showalter, *et al.* (1996, J. Pharmacol Exp Ther. 278(3), 989-99), with minor modifications. All assays were carried out in a final volume of 100 ul. Test compounds were re-suspended to 10 mM in DMSO, then serially diluted in 50 mM

Tris, pH 7.1, 3 mM $MgCl_2$, 1 mM EDTA, 50% DMSO. Aliquots (10 ul) of each diluted sample were then transferred into individual wells of a 96-well microtiter plate. Membranes from human CB_2 transfected CHO/Ki cells (Receptor Biology, Inc) were re-suspended in binding buffer (50 mM Tris, pH 7.1, 3 mM MgCl2, 1 mM EDTA, 0.1 % fatty acid free bovine serum albumin), then added to the binding reaction (~15 ug in 50 ul per assay). The reactions were initiated with the addition of [^{3}H] CP-55, 940 diluted in binding buffer (specific activity = 180 Ci/mmol; New England Nuclear, Boston, Mass.). The final ligand concentration in the binding reaction was 0.48 nM. Following incubation at room temperature for 2 hours, membranes were harvested by filtration through pretreated (0.5% polyethylenimine; Sigma P-3143) GF-C filter plates (Unifilter-96, Packard) using a TomTec™ Mach 3U 96-well cell harvester (Hamden, Ct). Plates were washed 10 times in 100 ul binding buffer, and the membranes allowed to air dry. Radioactivity on membranes was quantitated following addition of Packard Omniscint™ 20 scintillation fluid using a TopCount™ NXT Microplate Scintillation and Luminescence Counter (Packard, Meriden, Ct). Non-linear regression analysis was performed using Prism™ 20b. (GraphPad Software, San Diego, Ca).

Using the test procedures described above, representative compounds of formula I were found to have thrombin receptor IC_{50} values (*i.e.*, the concentration at which a 50% inhibition of thrombin receptor was observed) of 1 to 1000 nM, preferably 1-100 nM, more preferably 1-20 nM. CB_2 Ki values range from 1 to 1000 nM, preferably 1-200 nM, more preferably 1-100 nM.

We claim:

1. A compound represented by structural formula I:



formula I

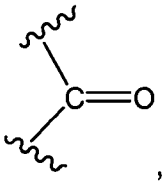
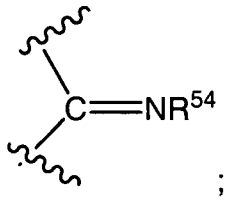
or a pharmaceutically acceptable salt, solvate, ester or prodrug of said compound, wherein

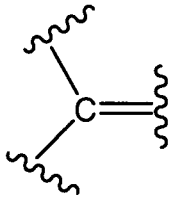
------ represents a double bond or a single bond, as permitted by the valency requirement; with the proviso that R^3 is absent when the carbon to which R^3 would be attached is part of a double bond;

B is $-(CH_2)_{n3}-$, $-(CH_2)-O-$, $-(CH_2)S-$, $-(CH_2)-NR^6-$, $-C(O)NR^6-$. $-NR^6C(O)-$,

 , $-(CH_2)_{n4}CR^{12}=CR^{12a}(CH_2)_{n5}-$ or $-(CH_2)_{n4}C\equiv C(CH_2)_{n5}-$, wherein n_3 is 0-5, n_4 and n_5 are independently 0-2, and R^{12} and R^{12a} are independently selected from the group consisting of hydrogen, alkyl and halogen;

A, E, G, M and J are independently selected from the group consisting of

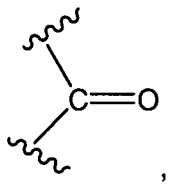
$-N(R^{54})-$, $-(CR^1R^2)-$, $-O-$,  , $-S-$, $-S(O)-$, $-S(O)_2-$ and  ;

X is  , -CH- or –N-, with the proviso that selection of A, G, M and X do not result in adjacent oxygen or sulfur atoms;

each n is 0, 1 or 2 with the proviso that all n variables cannot be 0;

Het is a mono-, bi- or tricyclic heteroaromatic group of 5 to 14 atoms comprised of 1 to 13 carbon atoms and 1 to 4 heteroatoms independently selected from the group consisting of N, O and S, with the proviso that there are no adjacent oxygen or sulfur atoms present in the heteroaromatic group, wherein a ring nitrogen can form an N-oxide or a quaternary group with an alkyl group, wherein Het is attached to B by a carbon atom ring member of Het, and wherein the Het group is substituted by 1 to 4 moieties, W, wherein each W is independently selected from the group consisting of hydrogen; alkyl; fluoroalkyl; difluoroalkyl; trifluoroalkyl; cycloalkyl; heterocycloalkyl; heterocycloalkyl substituted by alkyl or alkenyl; alkenyl; R^{21}-aryl; R^{21}-heteroaryl; R^{21}-arylalkyl; R^{21}-aryl-alkenyl; heteroaryl; heteroarylalkyl; heteroarylalkenyl; hydroxyalkyl; dihydroxyalkyl; aminoalkyl; alkylaminoalkyl; di-(alkyl)-aminoalkyl; thioalkyl; alkoxy; alkenyloxy; halogen; $-NR^4R^5$; -CN; -OH; $-C(O)OR^{17}$; $-COR^{16}$; $-OS(O_2)CF_3$; $-CH_2OCH_2CF_3$; alkylthio; $-C(O)NR^4R^5$; $-OCHR^6$-phenyl; phenoxyalkyl; $-NHCOR^{16}$; $-NHSO_2R^{16}$; biphenyl; $-OC(R^6)_2COOR^7$; $-OC(R^6)_2C(O)NR^4R^5$; alkoxy substituted by alkyl, amino or $-NHC(O)OR^{17}$; aryl;or alkyl optionally substituted with $-NR^1R^2$, $-NR^1COR^2$, $-NR^1CONR^1R^2$, $-NR^1C(O)OR^2$, $-NR^1S(O)_2R^2$, $-NR^1S(O)_2NR^1R^2$, -C(O)OH, $-C(O)OR^1$, $-CONR^1R^2$, hydroxyalkyl, alkyl or $-S(O)_2$-alkyl;$-C(O)NR^4R^5$ and heteroaryl; wherein adjacent carbons on the Het ring can optionally form a ring with a methylenedioxy group;

R^1 and R^2 are independently selected from the group consisting of hydrogen, alkyl, fluoroalkyl, difluoroalkyl, trifluoroalkyl, cycloalkyl, alkenyl, alkoxy, arylalkyl, arylalkenyl, heteroarylalkyl, heteroarylalkenyl, hydroxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, aryl and thioalkyl; or

R^1 and R^2 when attached to nitrogen, taken together, form a mono or bicyclic heterocyclic ring of 4 to 10 atoms, with 1-3 heteroatoms selected from –O-, -N-, -S-, -S(O)-, $-S(O)_2$- and  , with the proviso that S and O ring atoms are not adjacent to each other, where said heterocyclic ring is unsubstituted or substituted with one or more groups selected from alkyl, halogen, hydroxy, alkoxy, aryloxy and arylalkoxy;

R^3 is aralkoxy, aryloxy, heteroaryl, heteroaralkoxy, -CN, -NO_2, -O-aryl, -O-heteroaryl, N_3, $-C(O)NR^{18}R^{19}$, $-C(=NR^1)NR^1R^2$, $-N(R^1)C=(NR^1)NR^1R^2$; $-N=C(R^1)NR^1R^2$, $-NR^{18}C(O)R^{19}$, $-NR^{18}C(O)NR^{18}R^{19}$, $-NR^{18}C(O)OR^{19}$, $-NR^{18}S(O)_2R^{19}$, $-NR^{18}S(O)_2NR^{18}R^{19}$, $-NHNR^{18}R^{19}$, $-NR^{18}NR^{18}R^{19}$ or -alkyl-$NR^{18}R^{19}$;

R^6 is hydrogen, alkyl or phenyl;

R^7 is hydrogen or alkyl;

each R^{13} is independently selected from hydrogen, alkyl, cycloalkyl, haloalkyl, halogen, $-(CH_2)_{n6}NHC(O)OR^{16b}$, $-(CH_2)_{n6}NHC(O)R^{16b}$, $-(CH_2)_{n6}NHC(O)NR^4R^5$, $-(CH_2)_{n6}NHSO_2R^{16}$, $-(CH_2)_{n6}NHSO_2NR^4R^5$, and $-(CH_2)_{n6}C(O)NR^{28}R^{29}$, where n_6 is 0-4;

each R^{14} is independently selected from the group consisting of hydrogen, alkyl, -OH, alkoxy, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, halogen, haloalkyl, $-(CH_2)_{n6}NHC(O)OR^{16b}$, $-(CH_2)_{n6}NHC(O)R^{16b}$, $-(CH_2)_{n6}NHC(O)NR^4R^5$, $-(CH_2)_{n6}NHSO_2R^{16}$, $-(CH_2)_{n6}NHSO_2NR^4R^5$, and $-(CH_2)_{n6}C(O)NR^{28}R^{29}$ where n_6 is 0-4; where R^4 and R^5 are independently selected from the group consisting of hydrogen, alkyl, phenyl, benzyl and cycloalkyl, or R^4 and R^5 together can form a ring with the nitrogen to which they are attached, wherein said ring formed by R^4 and R^5 is optionally substituted with =O, OH, OR^1 or –C(O)OH; or

R^{13} and R^{14} taken together form a spirocyclic or a heterospirocyclic ring of 3-6 ring atoms, wherein said heterospirocyclic ring contains 2 to 5 carbon ring atoms and 1 or 2 hetero ring atoms selected from the group consisting of O, S and N;

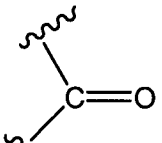
R^{16} is independently selected from the group consisting of hydrogen, alkyl, phenyl and benzyl;

R^{16a} is independently selected from the group consisting of hydrogen, alkyl, phenyl and benzyl;

R^{16b} is hydrogen, alkoxy, alkyl, alkoxyalkyl-, R^{22}-O-C(O)-alkyl-, cycloalkyl, R^{21}-aryl, R^{21}-arylalkyl, haloalkyl, alkenyl, halo substituted alkenyl, alkynyl, halo substituted alkynyl, R^{21}-heteroaryl, (R^{21}-heteroaryl)-alkyl-, (R^{21} –heterocycloalkyl)-alkyl-, $R^{28}R^{29}N$-alkyl-, $R^{28}R^{29}N$-C(O)-alkyl-, $R^{28}R^{29}N$-C(O)O-alkyl-, $R^{28}OC(O)N(R^{29})$-alkyl-, $R^{28}S(O)_2N(R^{29})$-alkyl-, $R^{28}R^{29}N$-C(O)-$N(R^{29})$-alkyl-, $R^{28}R^{29}N$-$S(O)_2N(R^{29})$-alkyl-, R^{28}-C(O)$N(R^{29})$-alkyl-, $R^{28}R^{29}N$-$S(O)_2$-alkyl-, $HOS(O)_2$-alkyl-, $(OH)_2P(O)_2$-alkyl-, R^{28}-S-alkyl-, R^{28}-$S(O)_2$-alkyl- or hydroxyalkyl;

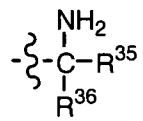
R^{17} is independently selected from the group consisting of hydrogen, alkyl, phenyl and benzyl;

R^{18} and R^{19} are hydrogen, alkyl, aryl, R^{21}-aryl, heteroaryl, cycloalkyl, heterocyclyl, alkoxyalkyl, haloalkoxyalkyl, aryloxyalkyl, arylalkoxyalkyl, heteroaryloxyalkyl, heteroarylalkoxyalkyl, cycloalkyloxyalkyl, (heterocyclyl)alkyloxyalkyl, alkoxyalkyloxyalkyl, -$S(O)_2$-alkyl, –$C(NH)NR^1R^2$ or alkyl substituted with one or two moieties selected from cycloalkyl, halogen, hydroxy, -NR^1R^2, -$NR^1C(O)R^2$, -$NR^1C(O)NR^1R^2$, -$NR^1C(O)OR^2$, -$NR^1S(O)_2R^2$, -$NR^1S(O)_2NR^1R^2$, -C(O)OH, -$C(O)OR^1$ and -$C(O)NR^1R^2$; or

R^{18} and R^{19} together with the nitrogen to which they are attached, form a mono or bicyclic heterocyclic ring of 4 to 10 atoms, having 1-3 hetero ring atoms selected from –O-, -N-, -S-, -S(O)-, -$S(O)_2$- and  , with the proviso that S and O atoms are not adjacent to each other, the ring being unsubstituted or substituted with one or more groups selected from alkyl, halogen, hydroxy, alkoxy, aryloxy, arylalkoxy, -NR^1R^2, -NR^1COR^2, -$NR^1C(O)NR^1R^2$, -$NR^1C(O)OR^2$, -$NR^1S(O)_2R^2$, -$NR^1S(O_2)NR^1R^2$, -$C(O)OR^1$, -$CONR^1R^2$ and alkyl substituted with -NR^1R^2, -NR^1COR^2, -$NR^1CONR^1R^2$, -$NR^1C(O)OR^2$, -$NR^1S(O)_2R^2$, -$NR^1S(O)_2NR^1R^2$, -$C(O)OR^1$ or -$CONR^1R^2$;

R^{21} is 1 to 3 moieties and each R^{21} is independently selected from the group consisting of hydrogen, -CN, -CF_3, -OCF_3, halogen, -NO_2, alkyl, -OH, alkoxy, alkylamino-, di-(alkyl)amino-, -$NR^{25}R^{26}$alkyl-, hydroxyalkyl-, -$C(O)OR^{17}$, -COR^{17}, -$NHCOR^{16}$, -$NHS(O)_2R^{16}$, -C(NH)-NH_2, -$NHS(O)_2CH_2CF_3$, -$C(O)NR^{25}R^{26}$, -NR^{25}-C(O)-$NR^{25}R^{26}$, -$S(O)R^{13}$, -$S(O)_2R^{13}$, –SR^{13}; -$SO_2NR^4R^5$ and -$CONR^4$ R^5; or two adjacent R^{21} moieties can form a methylenedioxy group;

R^{22} is hydrogen, alkyl, phenyl, benzyl, -COR^{16}, -$CONR^{18}R^{19}$, –COR^{23}, -$S(O)R^{31}$, -$S(O)_2R^{31}$, -$S(O_2)NR^{24}R^{25}$ or –$C(O)OR^{27}$;

R^{23} is  , wherein R^{35} and R^{36} are independently selected from the group consisting of hydrogen, alkyl, and R^{37}-substituted alkyl, wherein R^{37} is selected from the group consisting of HO-, HS-, CH_2S-, -NH_2, phenyl, p-hydroxyphenyl and indolyl; or R^{23} is alkyl; haloalkyl; alkenyl; haloalkenyl; alkynyl; cycloalkyl;

cycloalkylalkyl; cycloalkyl substituted by 1 to 3 substituents selected from the group consisting of alkoxyalkyl, alkyl, halogen, hydroxy, alkoxy, aryloxy, arylalkoxy, $-NR^1R^2$, $-NR^1C(O)R^2$, $-NR^1C(O)NR^1R^2$, $-NR^1C(O)OR^2$, $-NR^1S(O)_2R^2$, $-NR^1S(O)_2NR^1R^2$, $-C(O)OH$, $-C(O)OR^1$ and $-CONR^1R^2$; aryl; aralkyl; heteroaryl; heterocycloalkyl; alkyl substituted with $-NR^1R^2$, $-NR^1COR^2$, $-NR^1CONR^1R^2$, $-NR^1C(O)OR^2$, $-NR^1S(O_2)R^2$, $-NR^1S(O_2)NR^1R^2$, $-C(O)OH$, $-C(O)OR^1$, $-CONR^1R^2$ and $-SO_3H$;

R^{24}, R^{25} and R^{26} are independently selected from the group consisting of hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, halocycloalkyl, alkoxyalkyl, hydroxy and alkoxy;

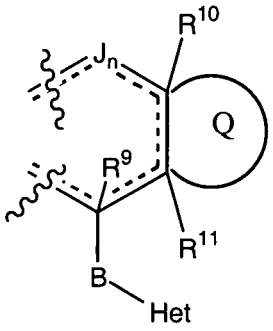
R^{27} is 1 to 3 moieties and each R^{27} is selected from the group consisting of hydrogen, alkyl, and cycloalkyl, wherein R^{27} is optionally substituted with -OH, -C(O)OH, halogen and alkoxy;

R^{28} and R^{29} are independently selected from the group consisting of hydrogen, alkyl, alkoxy, arylalkyl, heteroaryl, heteroarylalkyl, hydroxyalkyl, alkoxyalkyl, heterocyclyl, heterocyclylalkyl, and haloalkyl; or

R^{28} and R^{29} taken together form a spirocyclic or a heterospirocyclic ring having 3-6 ring atoms;

R^{32} and R^{33} are independently selected from the group consisting of hydrogen, R^{34}- alkyl, R^{34}-alkenyl, R^{34}-alkynyl, R^{40}-heterocycloalkyl, R^{38}-aryl, R^{38}-aralkyl, R^{42}-cycloalkyl, R^{42}-cycloalkenyl, -OH, $-OC(O)R^{43}$, $-C(O)OR^{43}$, $-C(O)R^{43}$, $-C(O)NR^{43}R^{44}$, $-NR^{43}R^{44}$, $-NR^{43}C(O)R^{44}$, $-NR^{43}C(O)NR^{44}R^{45}$, $-NHS(O)_2R^{43}$, $-OC(O)NR^{43}R^{44}$, R^{37}-alkoxy, R^{37}-alkenyloxy, R^{37}-alkynyloxy, R^{40}-heterocycloalkyloxy, R^{42}-cycloalkyloxy, R^{42}-cyclo-alkenyloxy, R^{42}-cycloalkyl-NH-, $-NHSO_2NHR^{16}$ and $-CH(=NOR^{17})$;

or R^{32} and R^{33} can be combined to form a ring structure Q, below

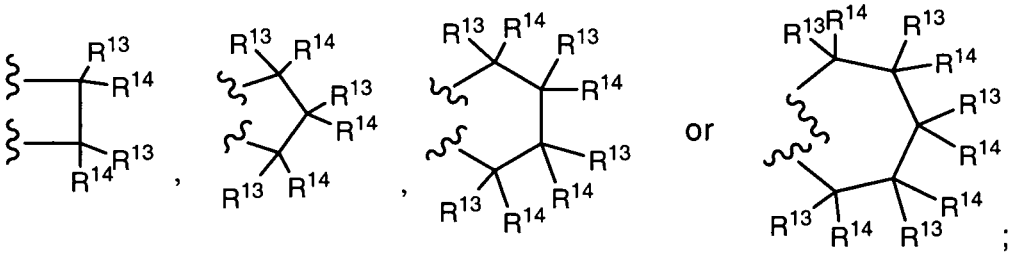


where

R^9 is hydrogen, OH, alkoxy, halogen or haloalkyl;

Q is fused R-substituted aryl, R-substituted heteroaryl, R-substituted heterocyclic ring of 4-8 atoms containing 1-3 heteroatoms selected from O, S, S(O), $S(O)_2$ and NR^{22} with the proviso that S and O cannot be adjacent to one another; or

Q is



wherein R^{10} and R^{11} are independently selected from the group consisting of R^1 and $-OR^1$, provided that when ring Q is aromatic and the carbon atoms bearing R^{10} and R^{11} are connected by a double bond, R^{10} and R^{11} are absent;

R is 1 to 5 moieties and each R is independently selected from the group consisting of hydrogen, alkyl, halogen, hydroxy, amino, alkylamino, dialkylamino, alkoxy, $-COR^{16}$, $-C(O)OR^{17}$, $-C(O)NR^4R^5$, $-SOR^{16}$, $-S(O_2)R^{16}$, $-NR^{16}COR^{16a}$, $-NR^{16}C(O)OR^{16a}$, $-NR^{16}CONR^4R^5$, $-NR^{16}S(O_2)NR^4R^5$, fluoroalkyl, difluoroalkyl, trifluoroalkyl, cycloalkyl, alkenyl, arylalkyl, arylalkenyl, heteroarylalkyl, heteroarylalkenyl, hydroxyalkyl, aminoalkyl, aryl and thioalkyl;

R^{34} is 1 to 3 moieties and each R^{34} is independently selected from the group consisting of hydrogen, halogen, -OH, alkoxy, R^{47}-aryl, alkyl-C(O)-, alkenyl-C(O)-, alkynyl-C(O)-, heterocycloalkyl, R^{39}-cycloalkyl, R^{39}-cycloalkenyl, $-OC(O)R^{43}$, $-C(O)OR^{43}$, $-C(O)R^{43}$, $-C(O)NR^{43}R^{44}$, $-NR^{43}R^{44}$, $-NR^{43}C(O)R^{44}$, $-NR^{43}C(O)NR^{44}R^{45}$, $-NHSO_2R^{43}$, $-OC(O)NR^{43}R^{44}$, R^{34}-alkenyloxy, R^{34}-alkynyloxy, R^{40}-heterocycloalkyloxy, R^{42}- cycloalkyloxy, R^{42}-cycloalkenyloxy, R^{42}-cycloalkyl-NH-, $-NHSO_2NHR^{16}$ and $-CH(=NOR^{17})$;

R^{38} is 1 to 3 moieties and each R^{38} is independently selected from the group consisting of hydrogen, heterocycloalkyl, halogen, $-C(O)OR^{48}$, -CN, $-C(O)NR^{49}R^{50}$, $-NR^{51}C(O)R^{52}$, $-OR^{48}$, cycloalkyl, cycloalkylalkyl, alkylcycloalkylalkyl, haloalkylcycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, and R^{52}-heteroaryl; or two R^{38} groups on adjacent ring carbons form a fused methylenedioxy group;

R^{39} is 1 to 3 moieties and each R^{39} is independently selected from the group consisting of hydrogen, halogen and alkoxy;

R^{40} is 1 to 3 moieties and each R^{40} is independently selected from the group consisting of hydrogen, R^{41}-alkyl, R^{41}-alkenyl and R^{41}-alkynyl;

R^{41} is hydrogen, -OH or alkoxy;

R^{42} is 1 to 3 moieties and each R^{42} is independently selected from the group consisting of hydrogen, alkyl, -OH, alkoxy and halogen;

R^{43}, R^{44} and R^{45} are independently selected from the group consisting of hydrogen, alkyl, alkoxyalkyl, R^{38}-arylalkyl, R^{46}-cycloalkyl, R^{53}-cycloalkylalkyl, R^{38}-aryl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl and heteroarylalkyl;

R^{46} is hydrogen, alkyl, hydroxyalkyl or alkoxy;

R^{47} is 1 to 3 moieties and each R^{47} is independently selected from the group consisting of hydrogen, alkyl, -OH, halogen, -CN, alkoxy, trihaloalkoxy, alkylamino, di(alkyl)amino, $-OCF_3$, hydroxyalkyl, -CHO, -C(O)alkylamino, -C(O)di(alkyl)amino, $-NH_2$, -NHC(O)alkyl and -N(alkyl)C(O)alkyl;

R^{48} is hydrogen, alkyl, haloalkyl, dihaloalkyl or trifluoroalkyl;

R^{49} and R^{50} are independently selected from the group consisting of hydrogen, alkyl, aralkyl, phenyl and cycloalkyl, or R^{49} and R^{50} together are $-(CH_2)_4$-, $-(CH_2)_5$- or $-(CH_2)_2$-NR^{39}-$(CH_2)_2$- and form a ring with the nitrogen to which they are attached;

R^{51} and R^{52} are independently selected from the group consisting of hydrogen, alkyl, aralkyl, phenyl and cycloalkyl, or R^{51} and R^{52} in the group $-NR^{39}C(O)R^{40}$, together with the nitrogen atoms to which they are attached, form a cyclic lactam having 5-8 ring members;

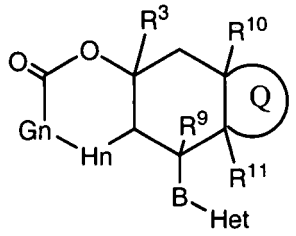
R^{53} is hydrogen, alkoxy, $-SOR^{16}$, $-SO_2R^{17}$, $-C(O)OR^{17}$, $-C(O)NR^{18}R^{19}$, alkyl, halogen, fluoroalkyl, difluoroalkyl, trifluoroalkyl, cycloalkyl, alkenyl, aralkyl, arylalkenyl, heteroarylalkyl, heteroarylalkenyl, hydroxyalkyl, aminoalkyl, aryl, thioalkyl, alkoxyalkyl or alkylaminoalkyl;

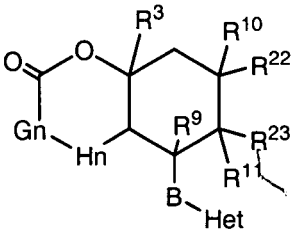
and

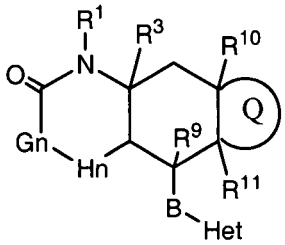
R^{54} is selected from the group consisting of hydrogen; alkyl; fluoroalkyl; difluoroalkyl; trifluoroalkyl; cycloalkyl; cycloalkyl substituted by 1 to 3 substituents selected from the group consisting of alkoxyalkyl, alkyl, halogen, hydroxy, alkoxy, aryloxy, arylalkoxy, $-NR^1R^2$, $-NR^1C(O)R^2$, $-NR^1C(O)NR^1R^2$, $-NR^1C(O)OR^2$, $-NR^1S(O)_2R^2$, $-NR^1S(O)_2NR^1R^2$, -C(O)OH, $-C(O)OR^1$ and $-CONR^1R^2$; alkenyl; alkoxy; arylalkyl; arylalkenyl; heteroarylalkyl; heteroarylalkenyl; hydroxy; alkoxy; hydroxyalkyl;

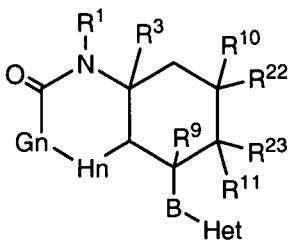
alkoxyalkyl; aminoalkyl; aryl; heteroaryl; thioalkyl and alkyl substituted by 1 to 3 subsituents selected from the group consisting of urea, sulfonamide, carboxamide, carboxylic acid, carboxylic ester and sulfonyl urea.

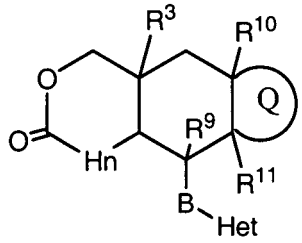
2. A compound of claim 1 wherein

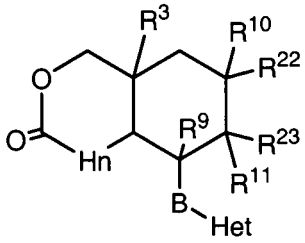

Ia

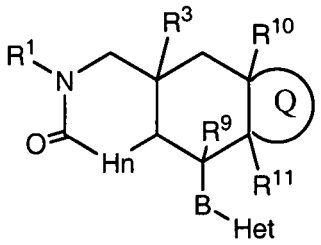

IIa

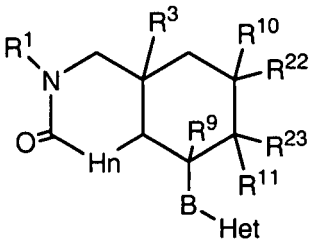

Ib

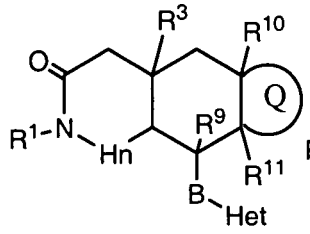

IIb

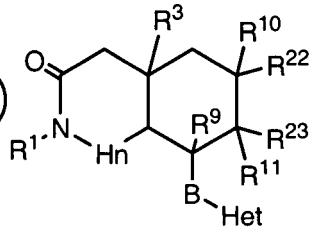

Ic

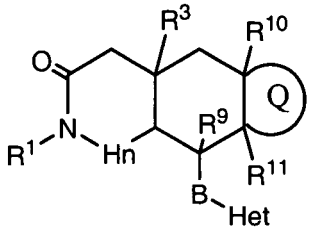

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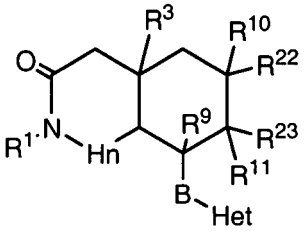

Id

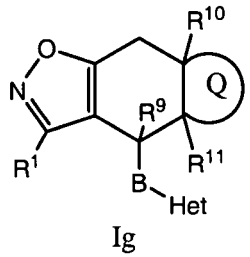

IId

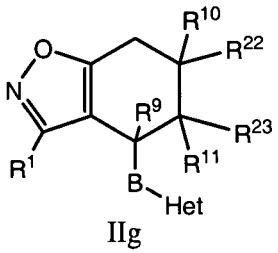

Ie

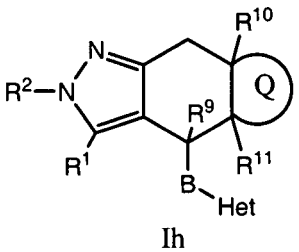

IIe

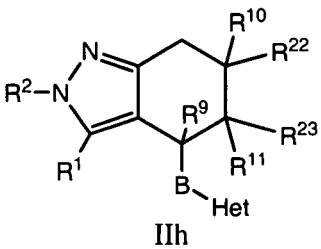

If

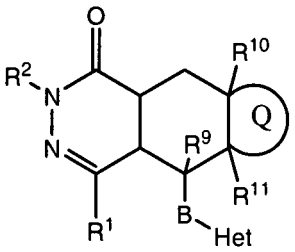

IIf

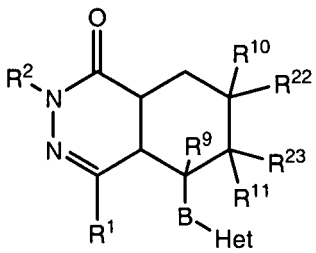

Ig

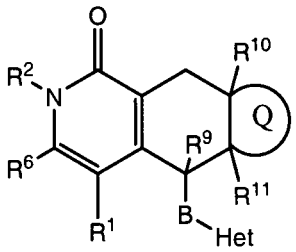

IIg

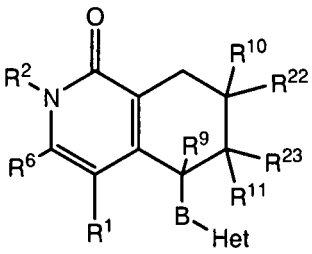

Ih


IIh

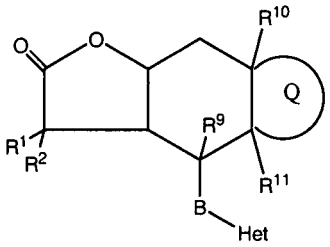

Ii

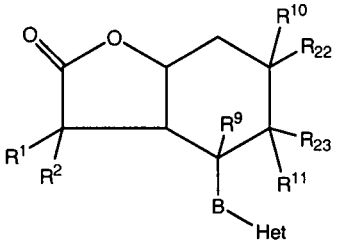

IIi

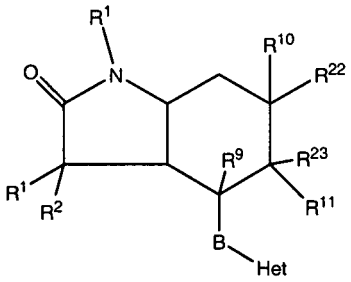

Ij


IIj

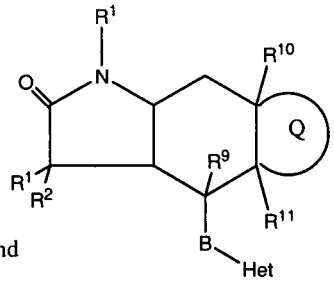
3. A compound of claim 2 wherein





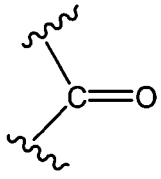


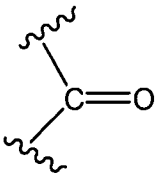
and



4. A compound of claim 1 wherein

E is -O-;

A is -O-,  or $-(CR^1R^2)-$;

G is  or $-(CR^1R^2)-$;

M is $-(CR^1R^2)-$;

X is –C(H)-;

R^3 is H;

R^9 is H;

R^{10} is H or alkyl;

R^{11} is H or alkyl;

R^{32} is H or alkyl;

R^{33} is H or alkyl;

B is $CR^{12}=CR^{12a}$-

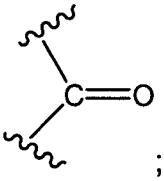
R^{12} and R^{12a} are H;

Het is aryl, aryl substituted by W, heteroaryl or heteroaryl substituted by W; and

W is aryl or aryl substituted with the 1 to 3 moieties comprising halogen, alkyl, $-CF_3$, -CN, -OH or -O-alkyl.

5. A compound of claim 1 wherein

E is -O-;

A is  ;

G is $-CH_2-$;

X is –C(H)-;

R^3 is H;

R^9 is H;

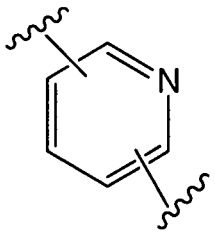
R^{10} is H or $-CH_3$;

R^{11} is H or $-CH_3$;

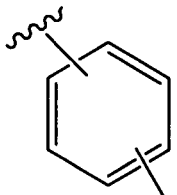
R^{32} is H or $-CH_3$;

R^{33} is H or $-CH_3$;

B is -CH=CH-;

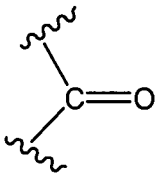
Het is  ;

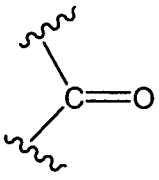
and

W is  CN.

6. A compound of claim 1 wherein

E is -O-;

A is -O-,  or $-(CR^1R^2)-$;

G is  or $-(CR^1R^2)-$;

M is $-(CR^1R^2)-$;

X is –C(H)-;

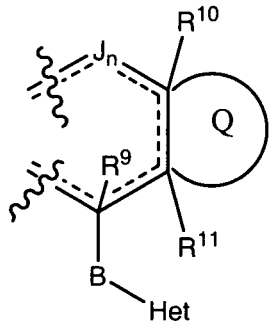
R^3 is H;

R^9 is H;

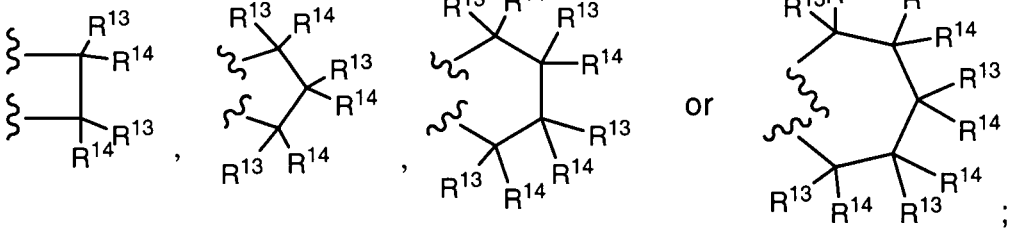
R^{10} is H or alkyl;

R^{11} is H or alkyl;

R^{32} and R^{33} are combined to form a ring structure Q, below



where Q is

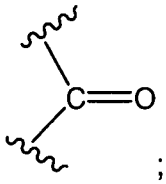


Het is aryl, aryl substituted by W, heteroaryl or heteroaryl substituted by W; and

W is aryl or aryl substituted with the 1 to 3 moieties comprising halogen, alkyl, $-CF_3$, -CN, -OH or -O-alkyl.

7. A compound of claim 1 wherein

E is -O-;

A is  ;

G is $-CH_2-$;

X is –C(H)-;

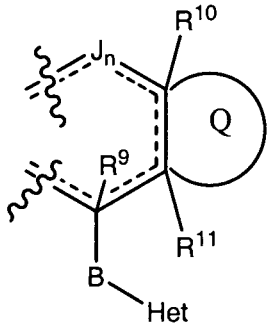
R^3 is H;

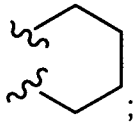
R^9 is H;

R^{10} is H or $-CH_3$;

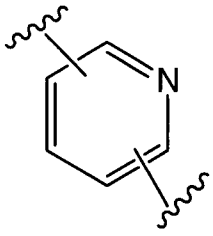
R^{11} is H or $-CH_3$;

R^{32} and R^{33} are combined to form a ring structure Q, below

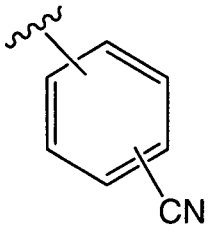
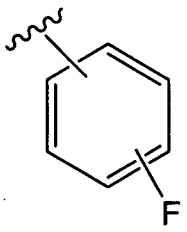
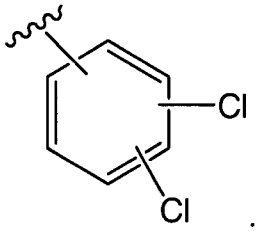


where Q is  ;

B is -CH=CH-;

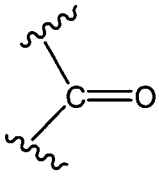
Het is  ;

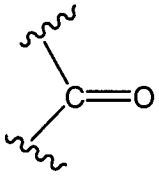
and

W is   or  .

8. A compound of claim 1 wherein

E is –N(H)- or –N(alkyl)-;

A is –N(H)-, –N(alkyl)-,  or $-(CR^1R^2)-$;

G is  or $-(CR^1R^2)-$;

M is $-(CR^1R^2)-$;

X is –C(H)-;

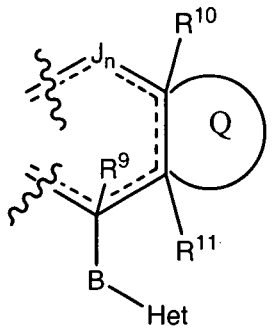
R^3 is H;

R^9 is H;

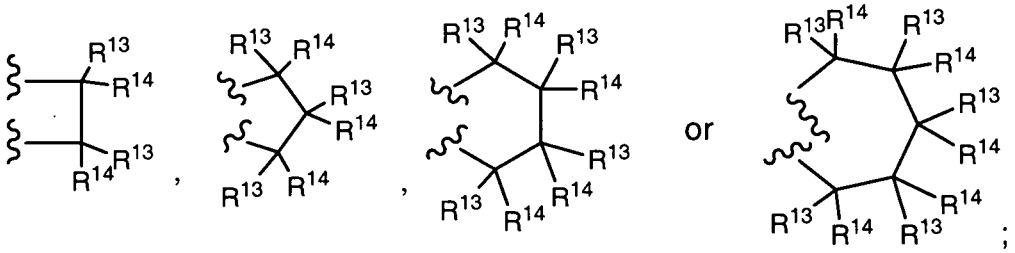
R^{10} is H or alkyl;

R^{11} is H or alkyl;

R^{32} and R^{33} are combined to form a ring structure Q, below



where Q is

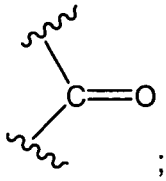


Het is aryl, aryl substituted by W, heteroaryl or heteroaryl substituted by W; and

W is aryl or aryl substituted with the 1 to 3 moieties comprising halogen, alkyl, $-CF_3$, -CN, -OH or -O-alkyl.

9. A compound of claim 1 wherein

E is –N(H)- or –N(alkyl)-;



A is ;

G is $-CH_2-$;

X is –C(H)-;

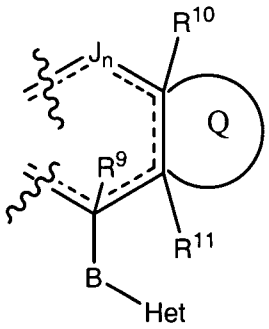
R^3 is H;

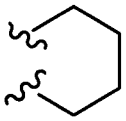
R^9 is H;

R^{10} is H or $-CH_3$;

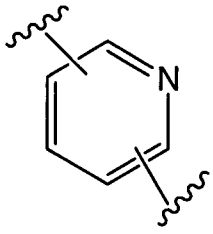
R^{11} is H or $-CH_3$;

R^{32} and R^{33} are combined to form a ring structure Q, below



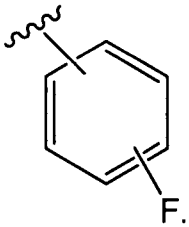
where Q is  ;

B is -CH=CH-;

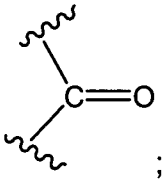
Het is 

;

and

W is 

10. A compound of claim 1 wherein

E is 

;

A is –N(H)-or –N(alkyl)-;

G is –N=;

M is $-(CR^1R^2)-$;

X is –C(H)-;

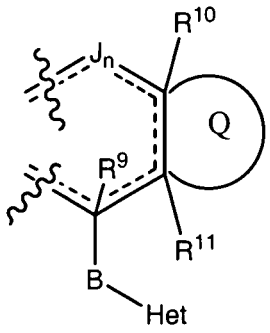
R^3 is H;

R^9 is H;

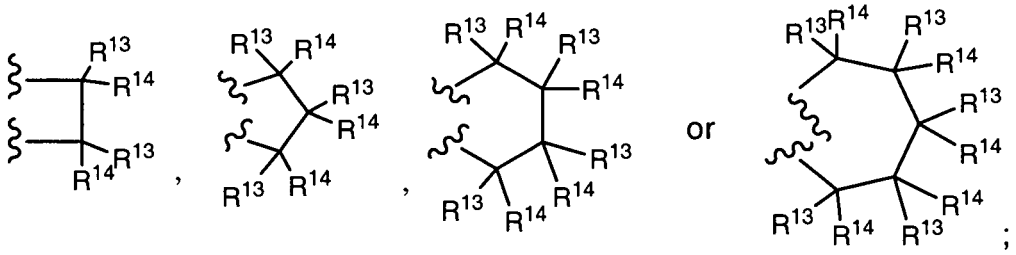
R^{10} is H or alkyl;

R^{11} is H or alkyl;

R^{32} and R^{33} are combined to form a ring structure Q, below



where Q is



;

Het is aryl, aryl substituted by W, heteroaryl or heteroaryl substituted by W; and

W is aryl or aryl substituted with the 1 to 3 moieties comprising halogen, alkyl, $-CF_3$, -CN, -OH or -O-alkyl.

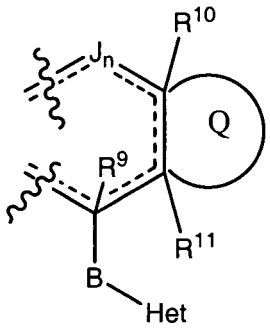
11. A compound of claim 10 wherein

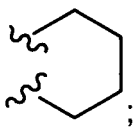
A is $-N(H)-$ or $-N(CH_3)-$;

R^{10} is H or $-CH_3$;

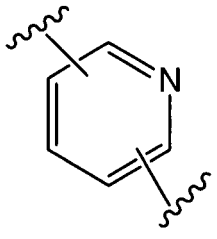
R^{11} is H or $-CH_3$;

R^{32} and R^{33} are combined to form a ring structure Q, below

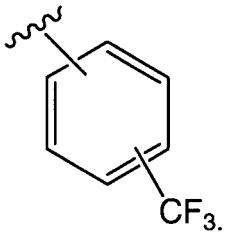


where Q is  ;

B is -CH=CH-;

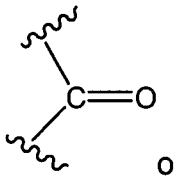
Het is  ;

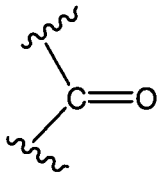
and

W is  .

12. A compound of claim 1 wherein

E is -O-;

A is -O-,  or $-(CR^1R^2)-$;

G is  or $-(CR^1R^2)-$;

M is $-(CR^1R^2)-$;

X is –C(H)–;

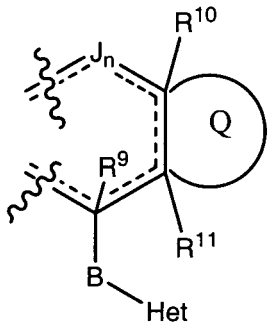
R^3 is H;

R^9 is H;

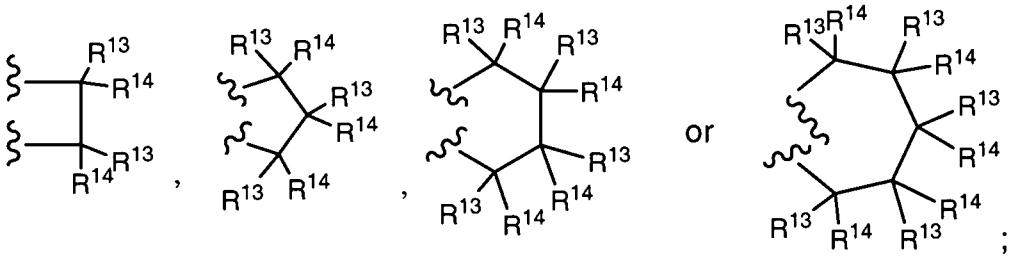
R^{10} is H or alkyl;

R^{11} is H or alkyl;

R^{32} and R^{33} are combined to form a ring structure Q, below



where Q is

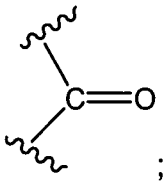


Het is aryl, aryl substituted by W, heteroaryl or heteroaryl substituted by W; and

W is aryl or aryl substituted with the 1 to 3 moieties comprising halogen, alkyl, $-CF_3$, -CN, -OH or -O-alkyl.

13. A compound of claim 1 wherein

E is -O-;

A is  ;

G is $-CH(CH_3)-$;

X is –C(H)-;

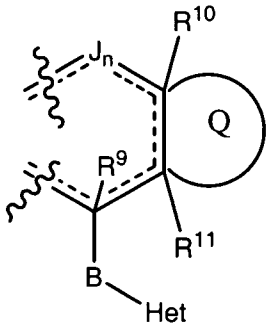
R^3 is H;

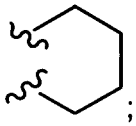
R^9 is H;

R^{10} is H or $-CH_3$;

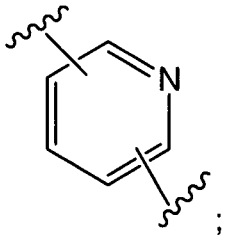
R^{11} is H or $-CH_3$;

R^{32} and R^{33} are combined to form a ring structure Q, below

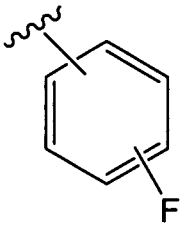
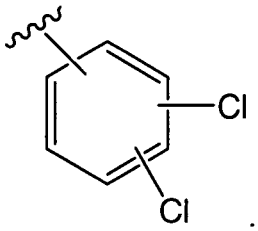


where Q is  ;

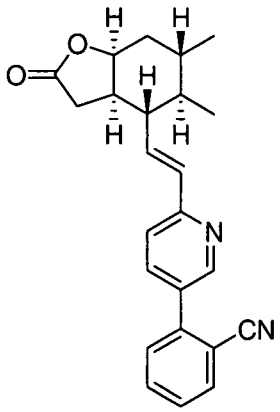
B is -CH=CH-;

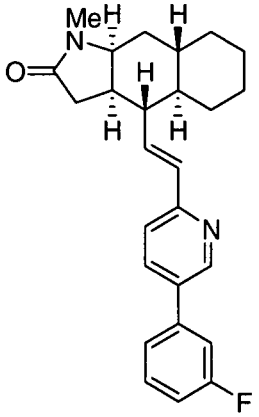
Het is  ;

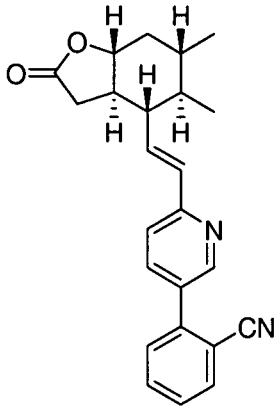
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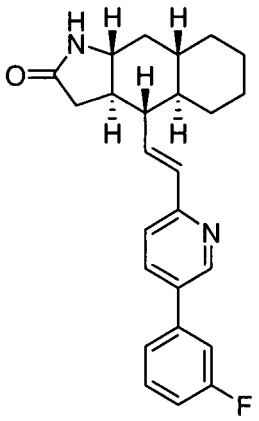
W is  or  .

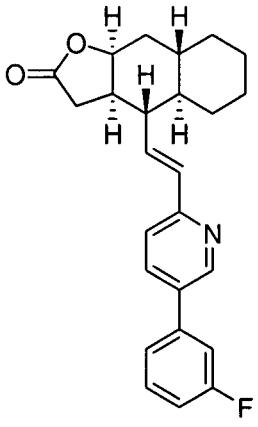
14. A compound selected from the group consisting of:

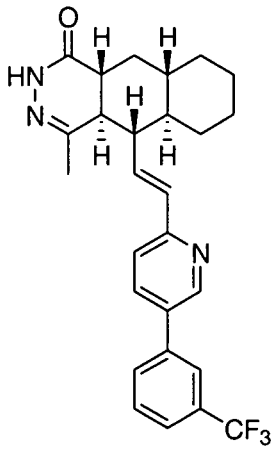


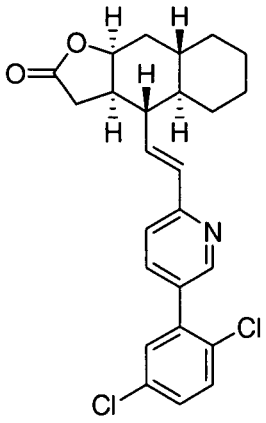


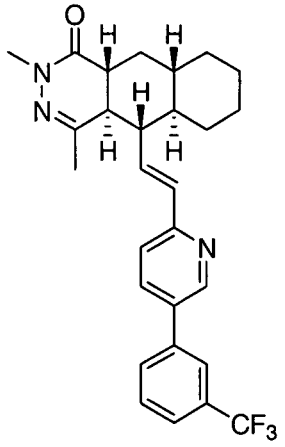


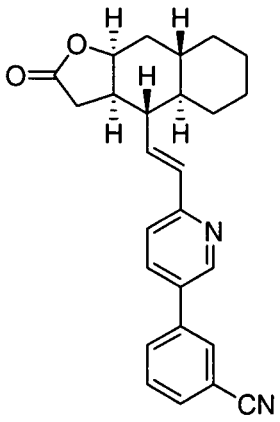


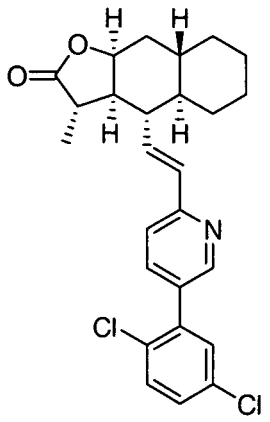


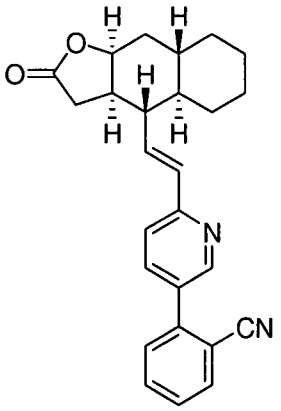


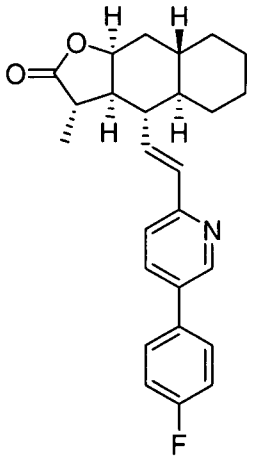


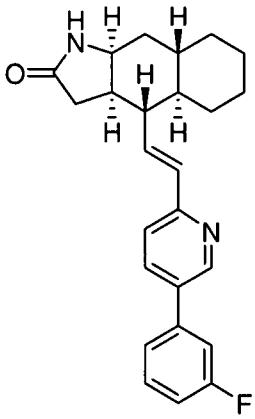




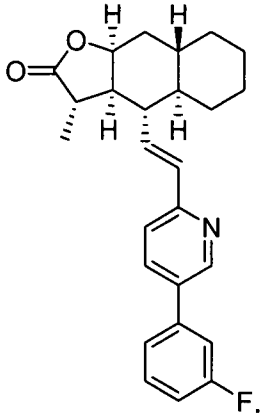




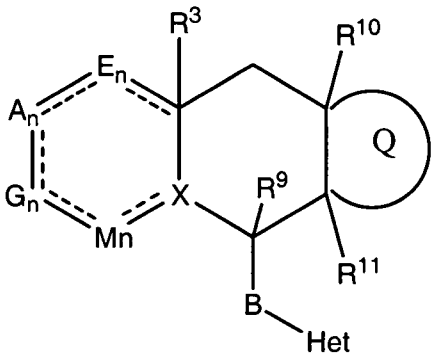




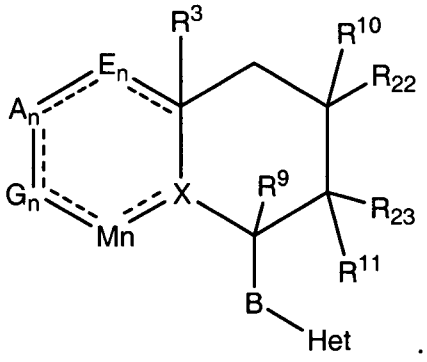
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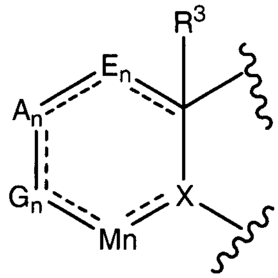
15. A compound of claim 1 wherein



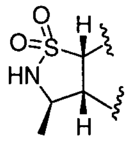
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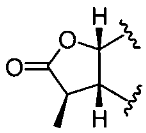


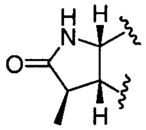
16. A compound of claim 15 wherein

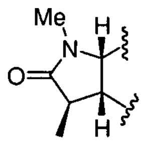


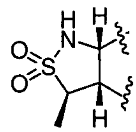
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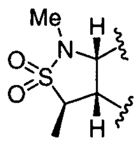


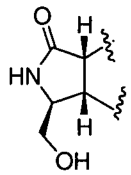


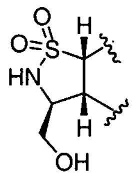


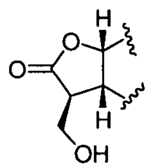


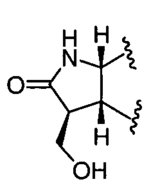


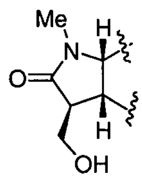


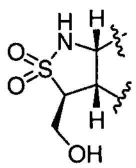


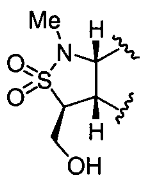


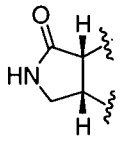
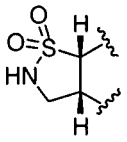
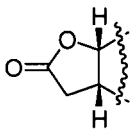
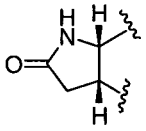
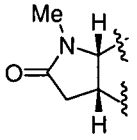
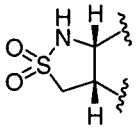
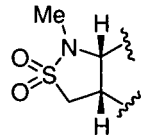
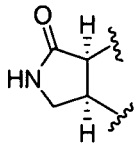
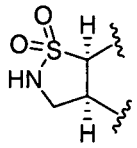
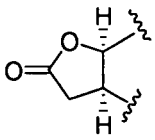
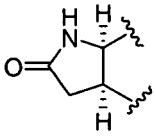
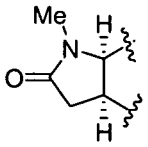
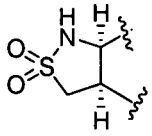
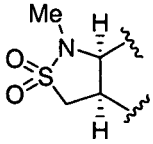


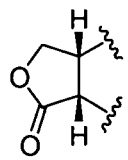
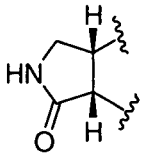
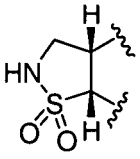
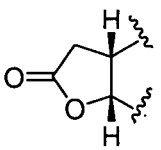
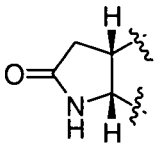
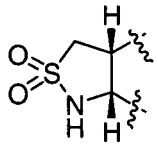
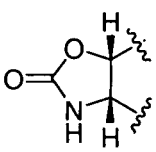
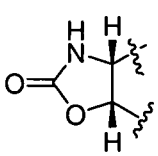
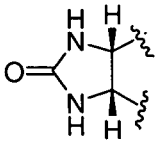


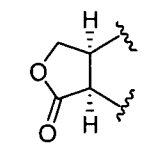
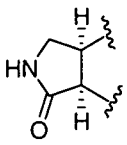
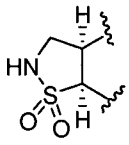
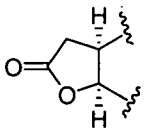
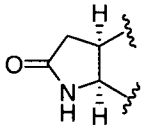
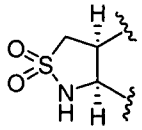
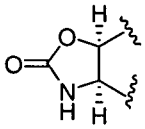
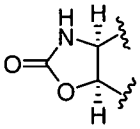
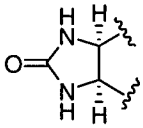
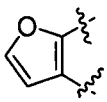
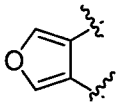
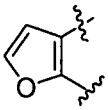
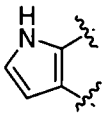
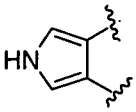
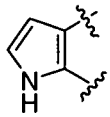
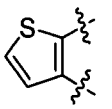
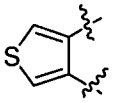
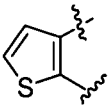
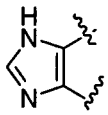
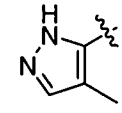
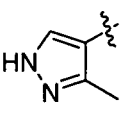


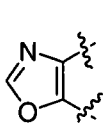
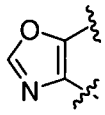
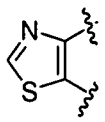
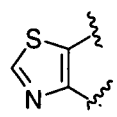


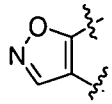
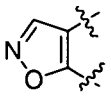
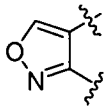
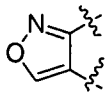
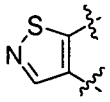
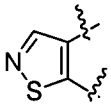
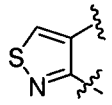
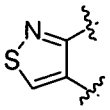
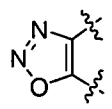
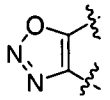
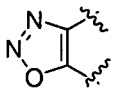
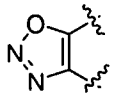
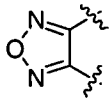
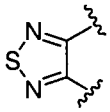
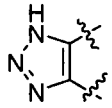
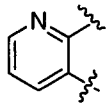
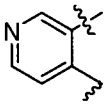
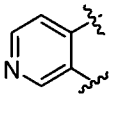
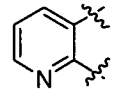
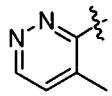


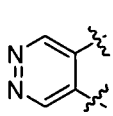
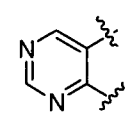
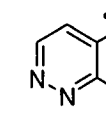















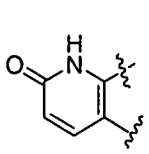
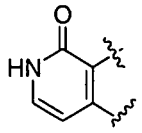
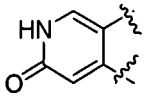
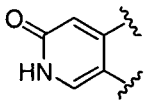
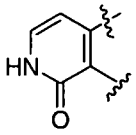































5





or


17. A compound of claim 16 wherein

R^3 is absent or R^3 is H;

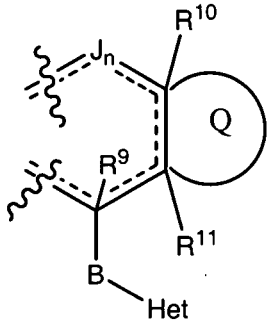
R^9 is H;

R^{10} is H or alkyl;

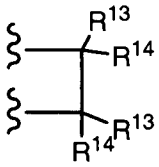
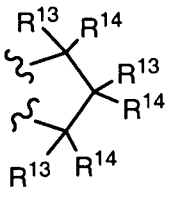
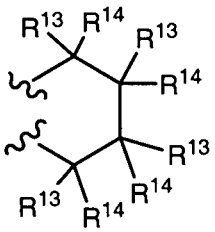
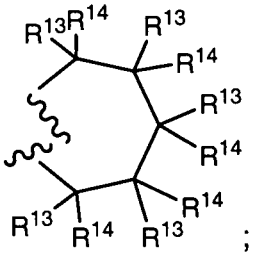
R^{11} is H or alkyl;

R^{32} is H or alkyl;

R^{33} is H or alkyl; or R^{32} and R^{33} are combined to form a ring structure Q, below



where Q is


,

,

or

;

B is -CH=CH-

Het is aryl, aryl substituted by W, heteroaryl or heteroaryl substituted by W; and

W is aryl or aryl substituted with the 1 to 3 moieties comprising halogen, alkyl, $-CF_3$, -CN, -OH or -O-alkyl.

18. A compound of claim 17 wherein

R^3 is H;

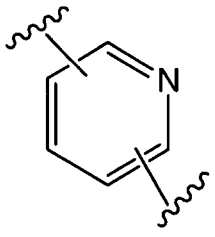
R^9 is H;

R^{10} is H or $-CH_3$;

R^{11} is H or $-CH_3$;

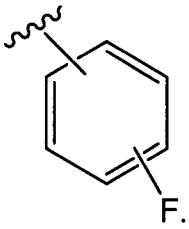
R^{32} is H or $-CH_3$;

R^{33} is H or $-CH_3$;

Het is 

;

and

W is 

.

19. A compound of claim 17 wherein

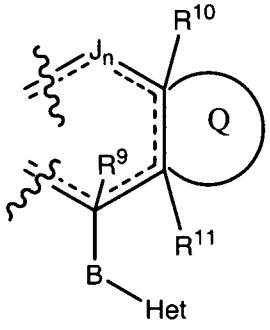
R^3 is absent or R^3 is H;

R^9 is H;

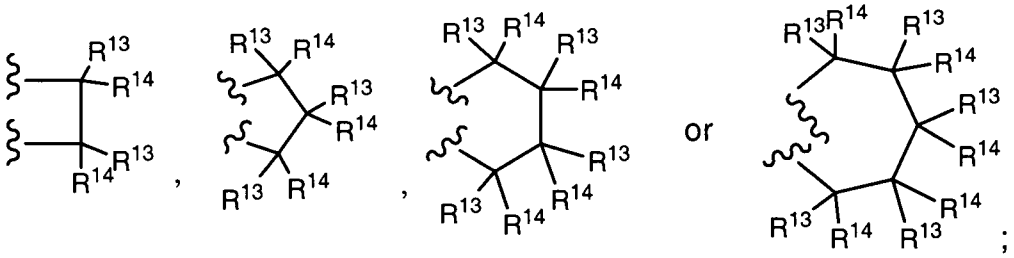
R^{10} is H;

R^{11} is H;

R^{32} and R^{33} are combined to form a ring structure Q, below



where Q is



R^{13} is $(-CH_2)_{n6}NHC(O)OR^{16b}$;

R^{16b} is alkyl;

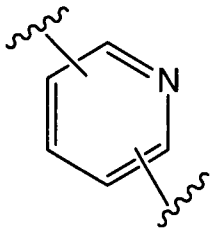
B is -CH=CH-

Het is aryl, aryl substituted by W, heteroaryl or heteroaryl substituted by W; and

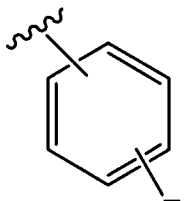
W is aryl or aryl substituted with the 1 to 3 moieties comprising halogen, alkyl, $-CF_3$, -CN, -OH or -O-alkyl.

20. A compound of claim 19 wherein

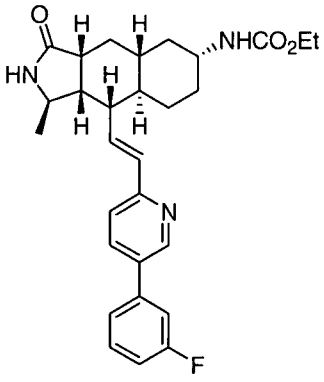
R^{13} is $-NHC(O)OCH_2CH_3$;

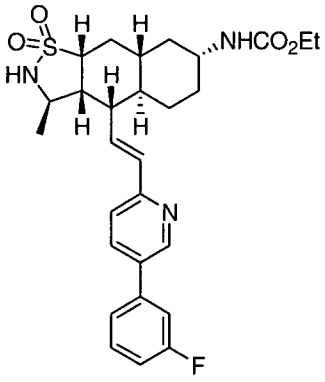
Het is  ;

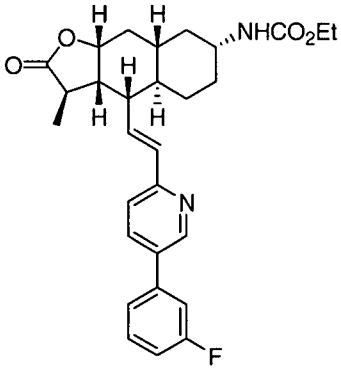
and

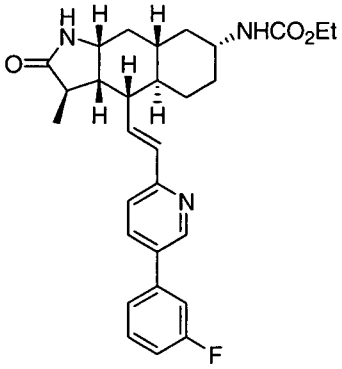
W is  F.

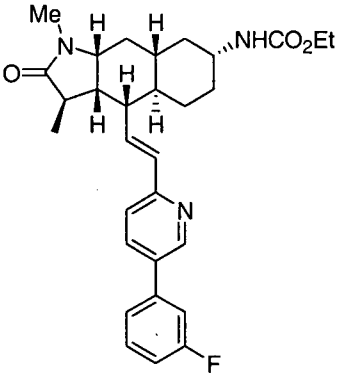
21. A compound selected from the group consisting of:

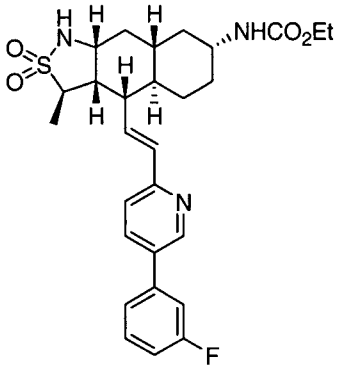


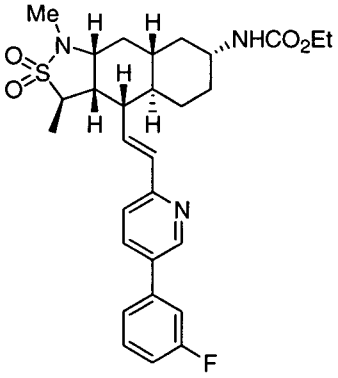


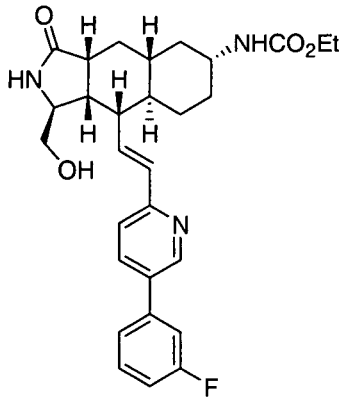


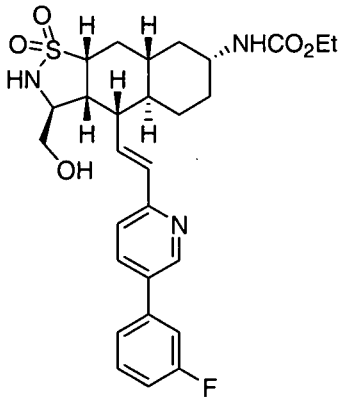


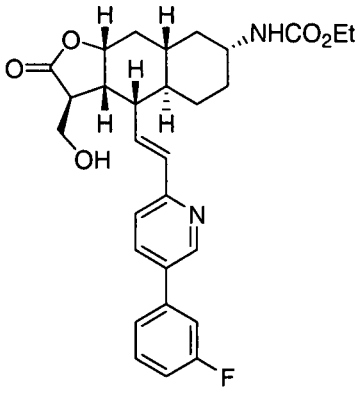


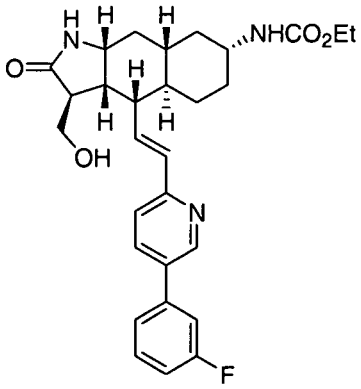


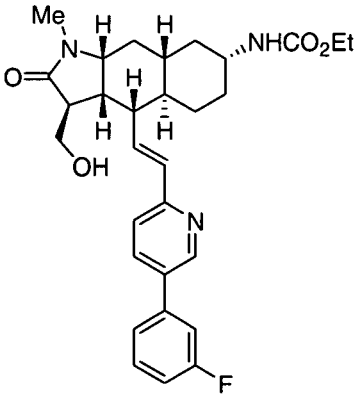


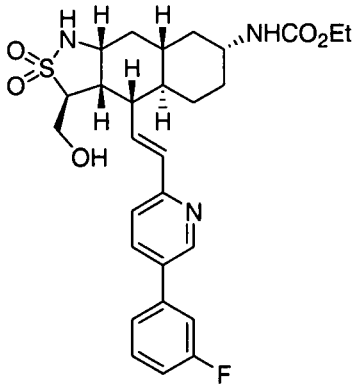


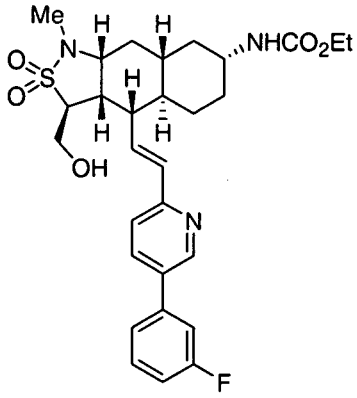


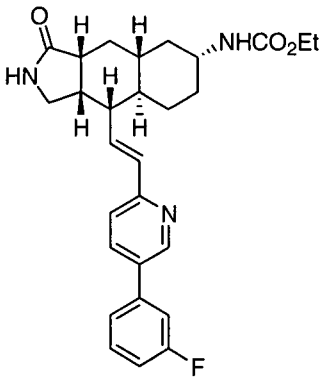


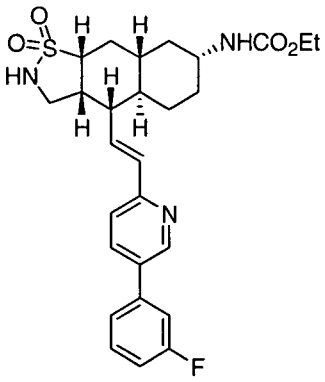


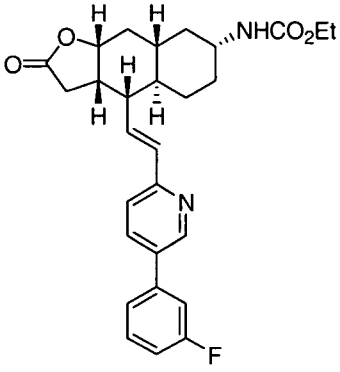


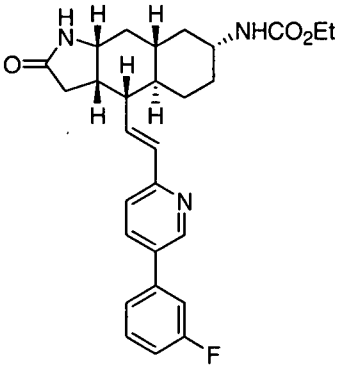


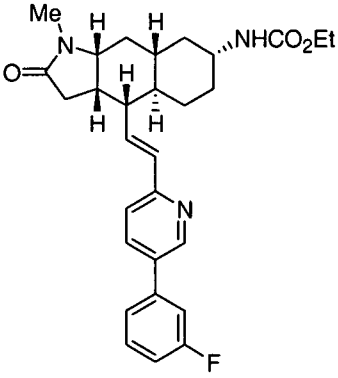


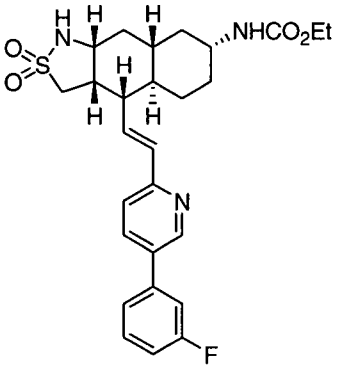


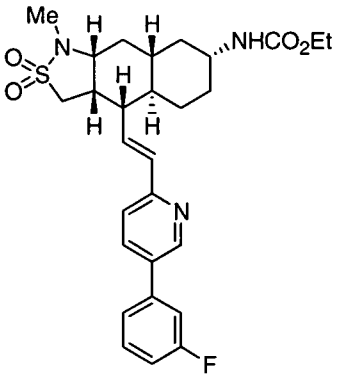


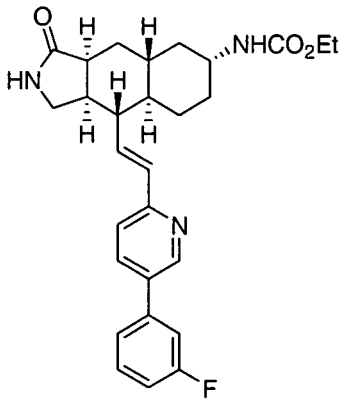


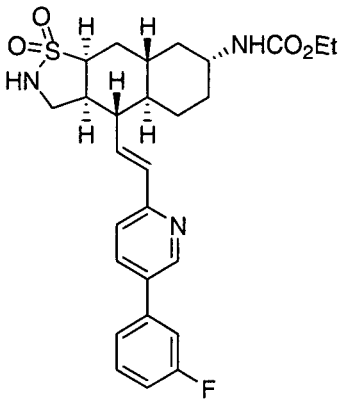


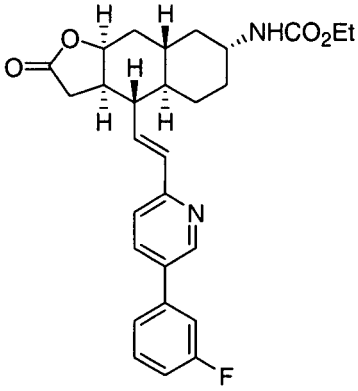


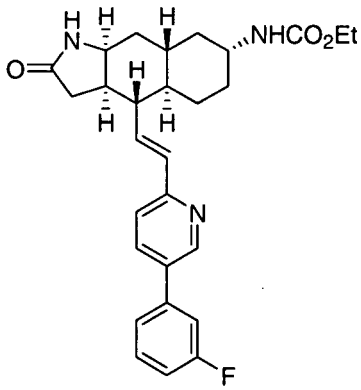


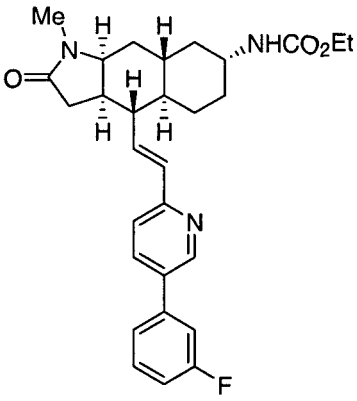


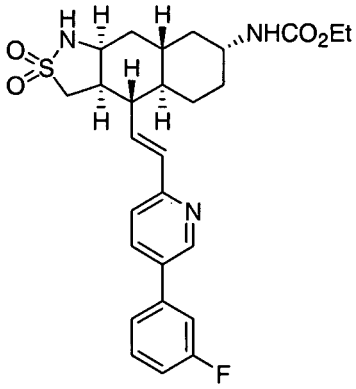


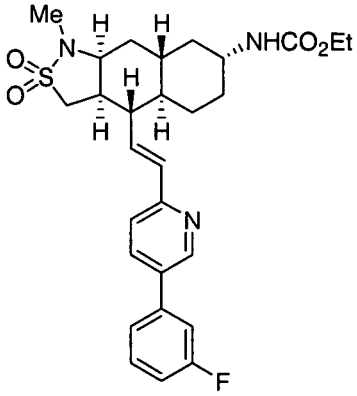


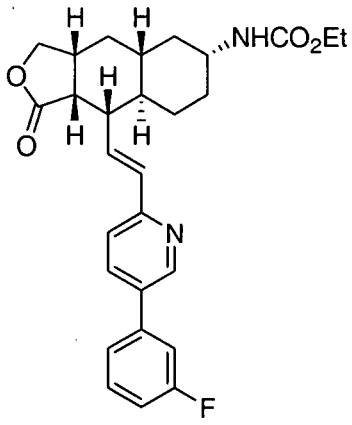


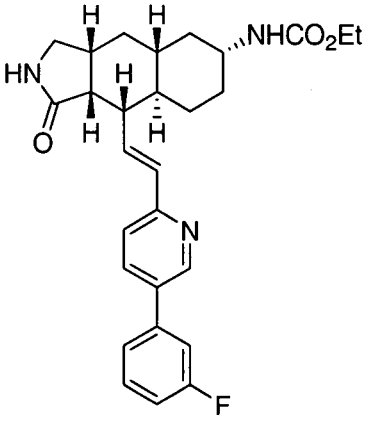


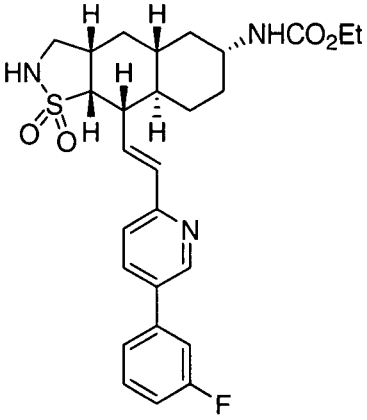


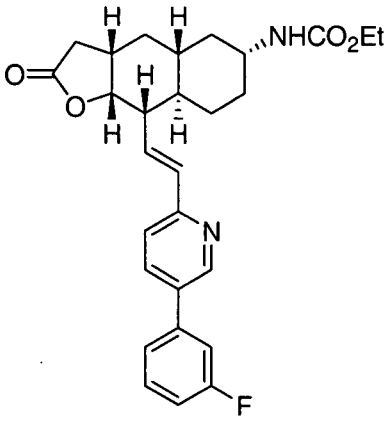


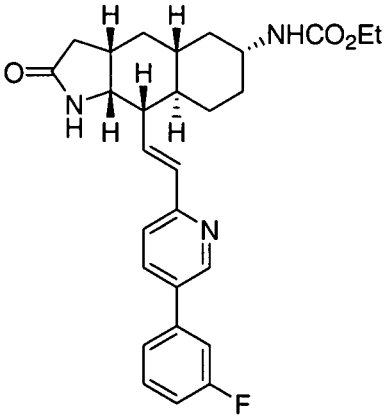


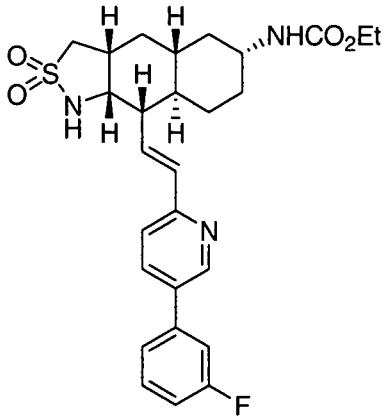


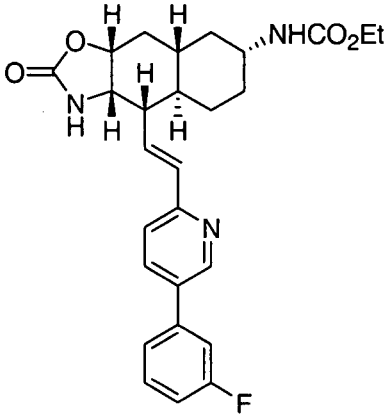


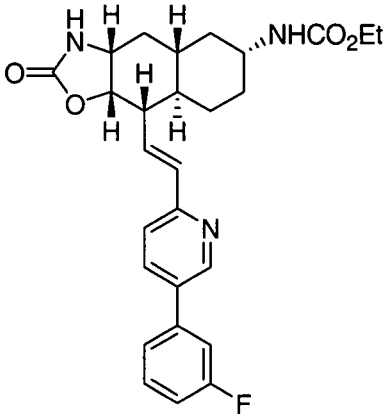


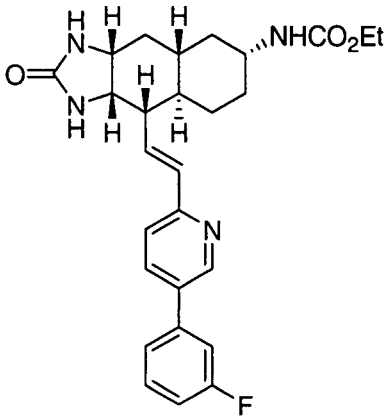


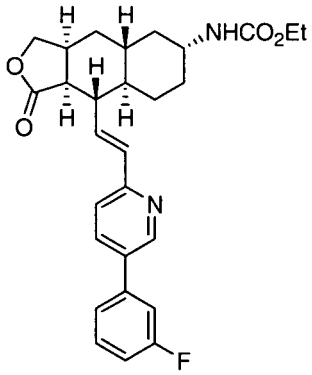


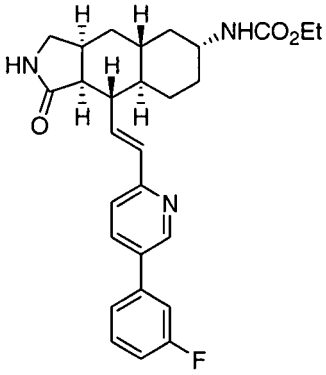


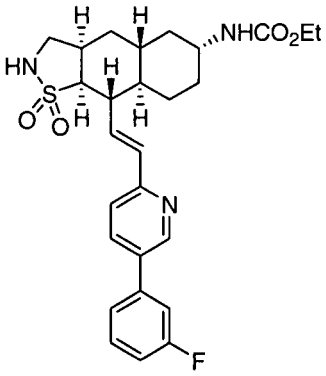


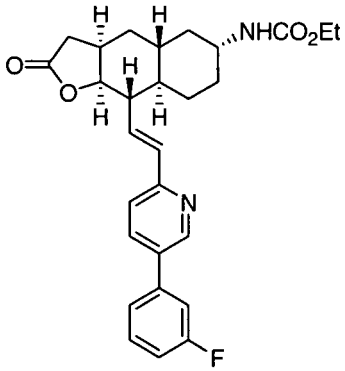


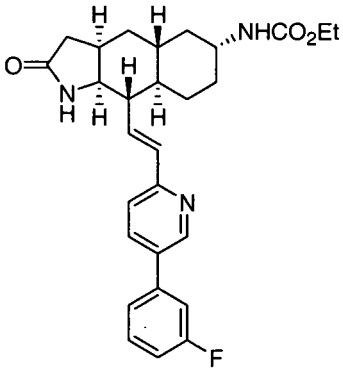


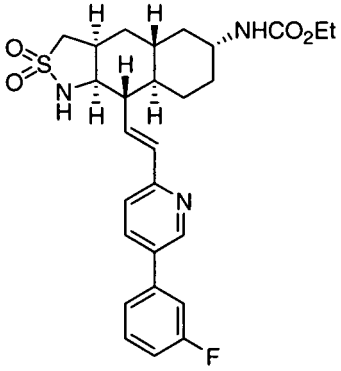


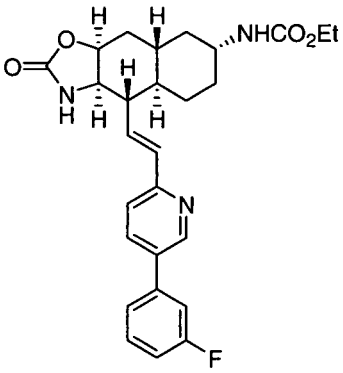


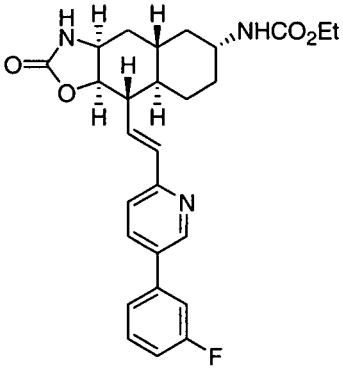


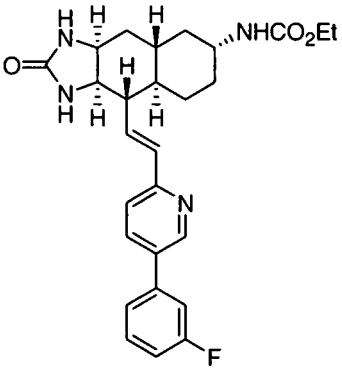




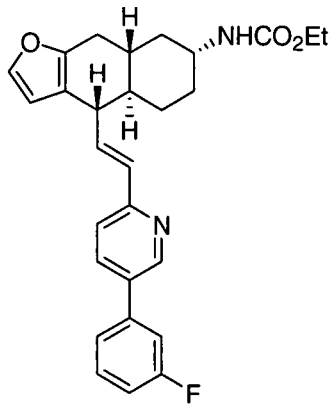
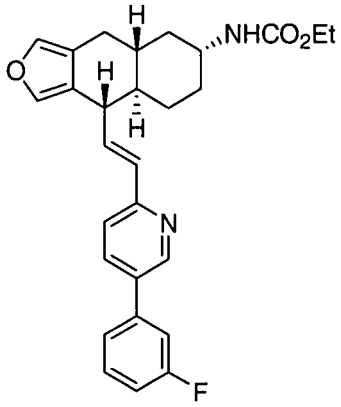
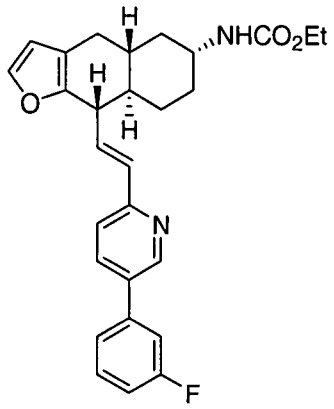
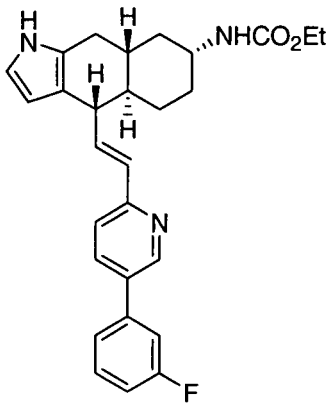
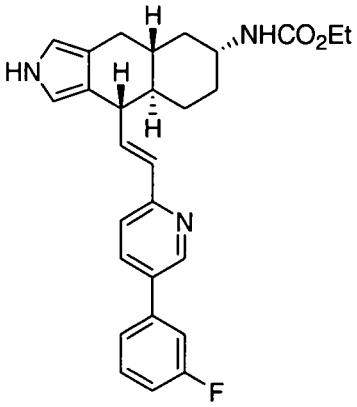
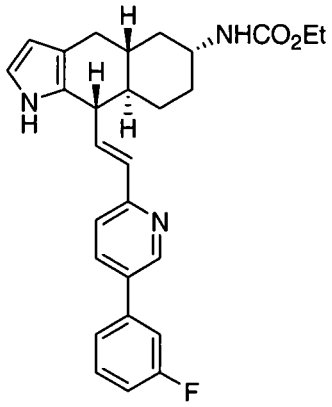
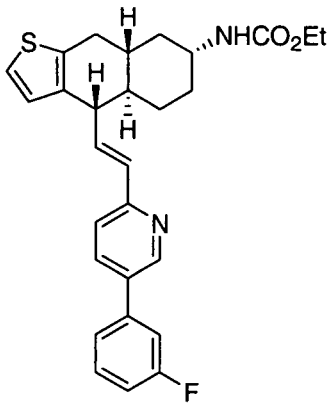
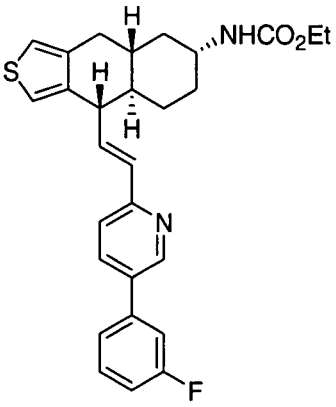
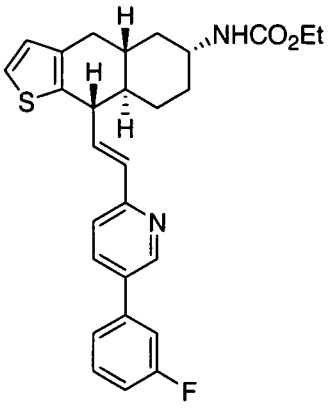


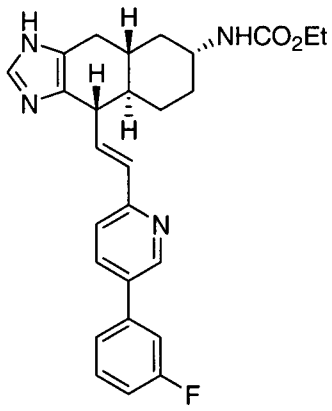


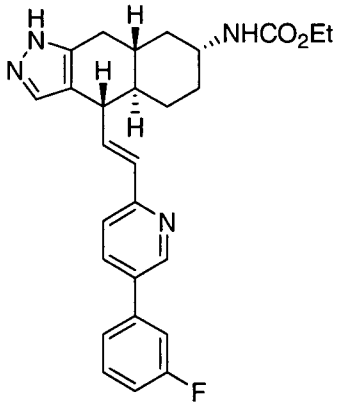


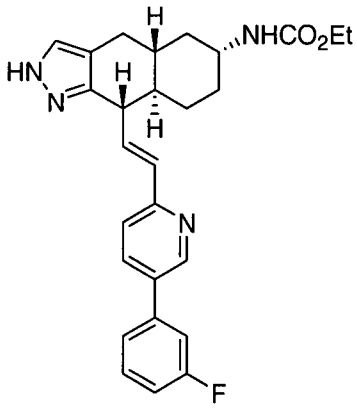


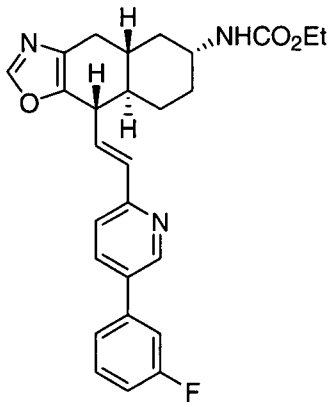
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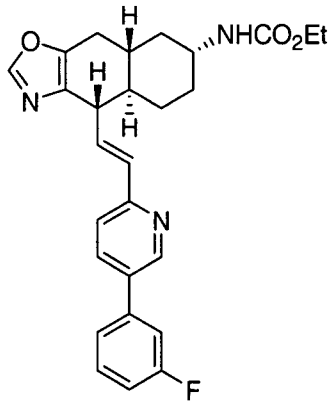










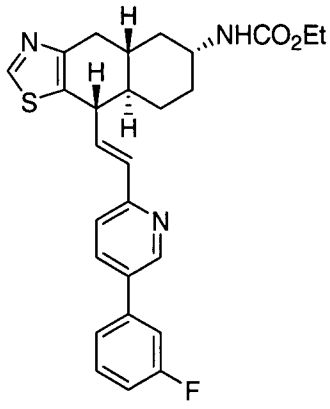


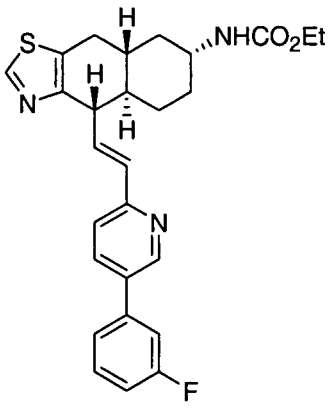




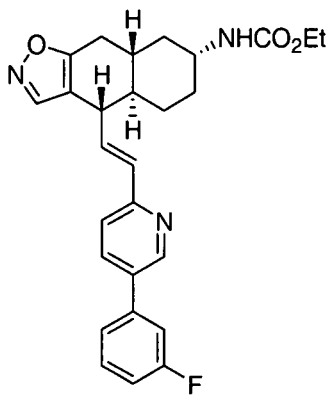


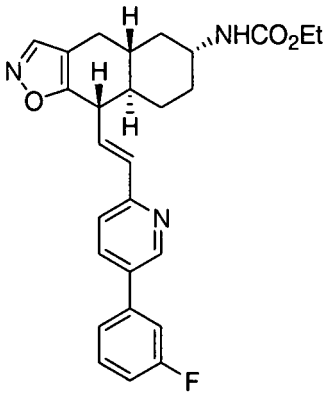


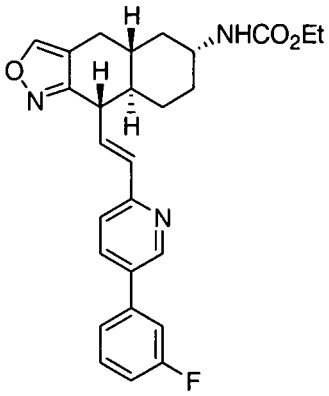


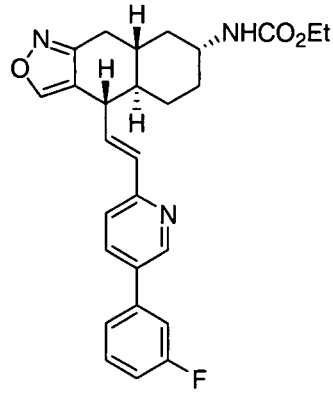


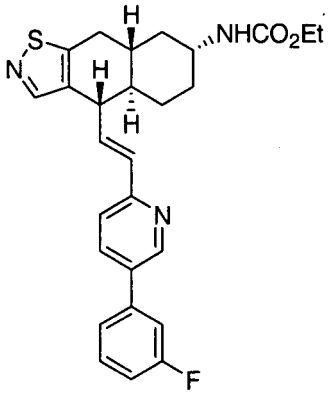
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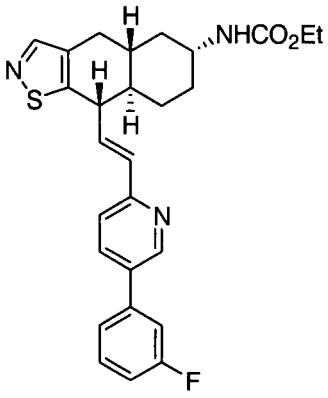


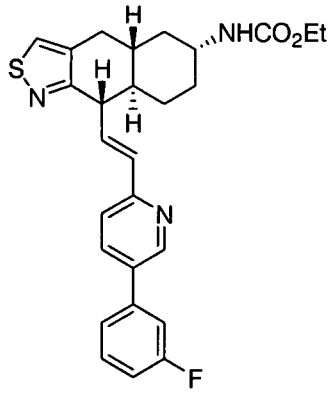


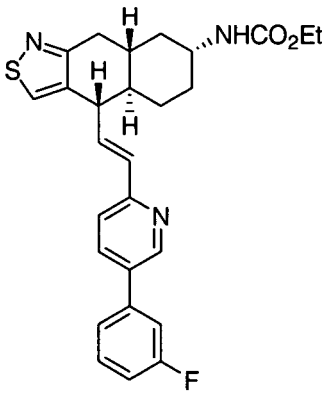






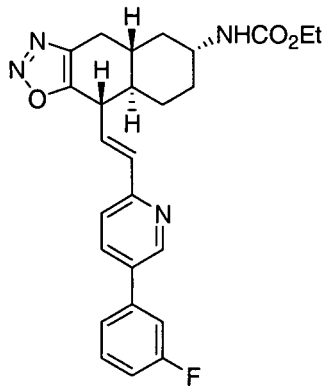


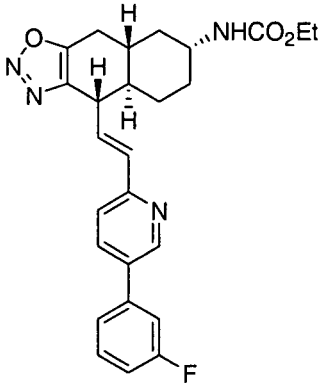


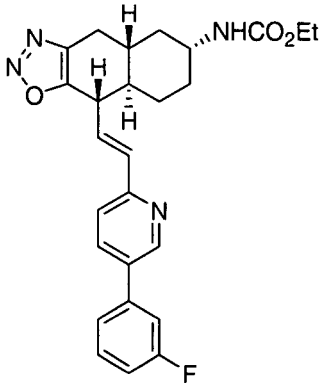


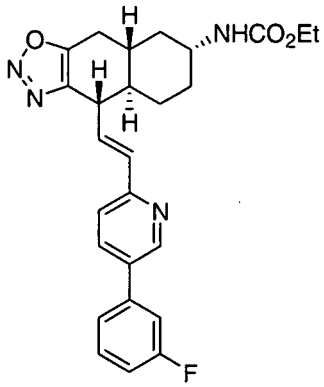
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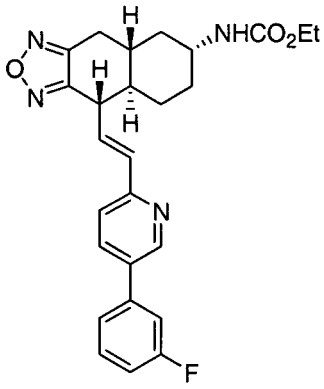
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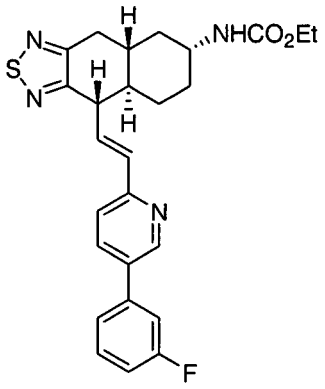


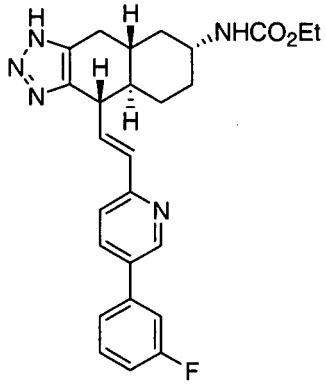


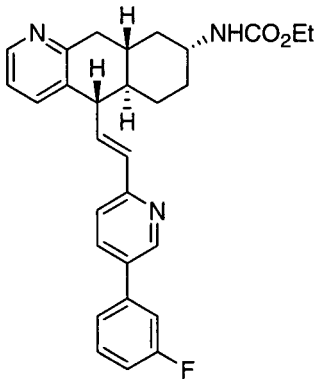


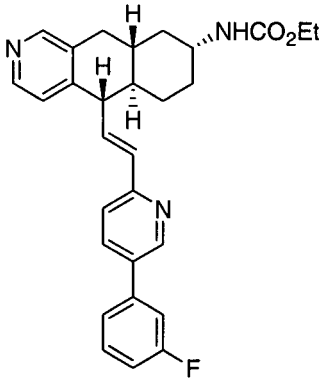


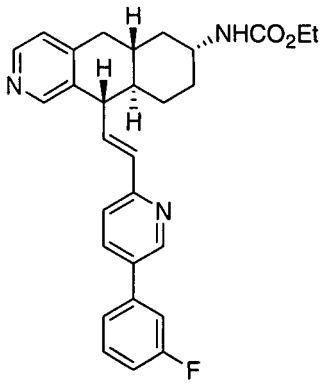


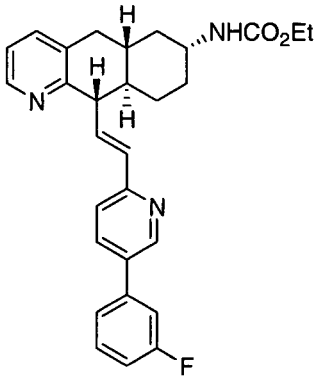


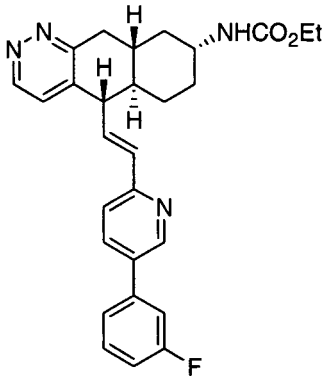


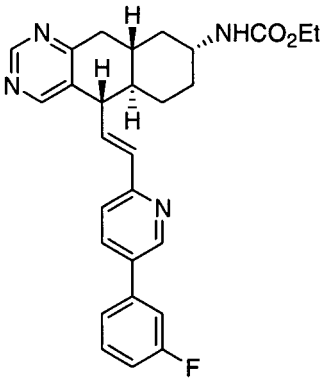


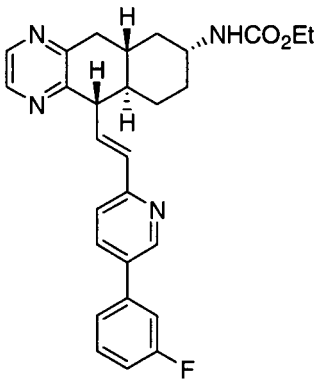


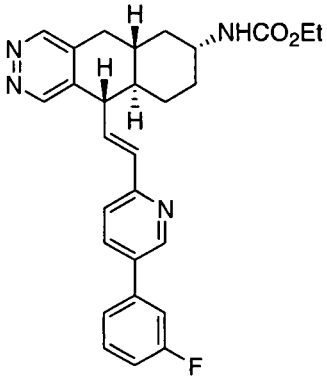


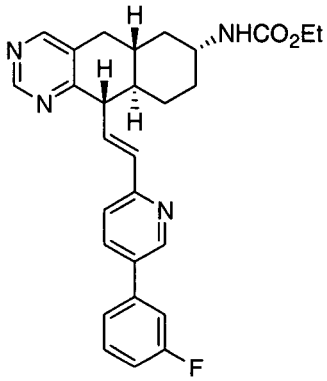


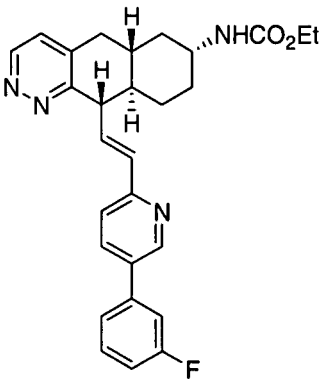


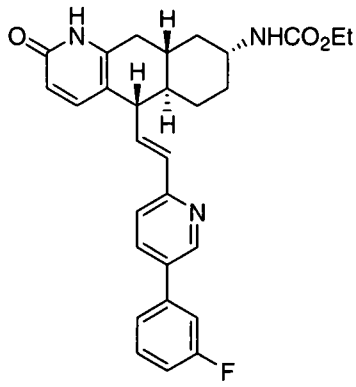


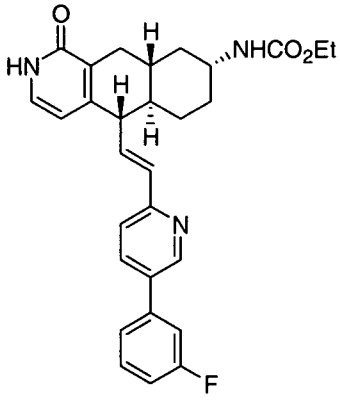


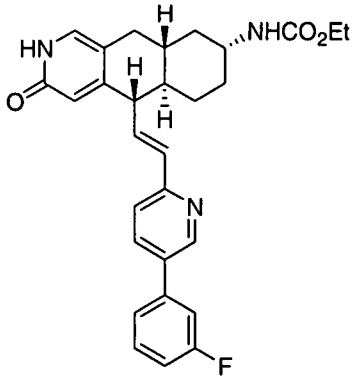


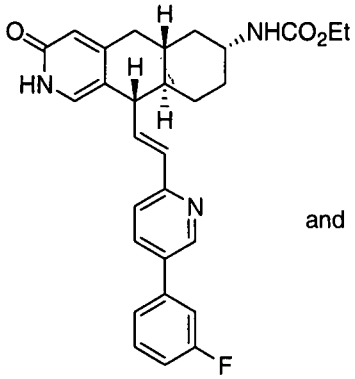




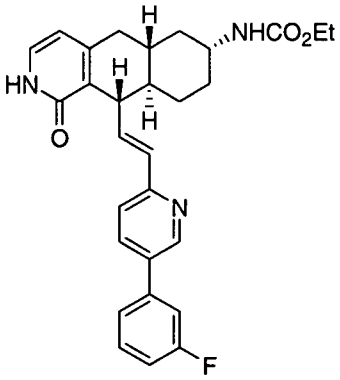




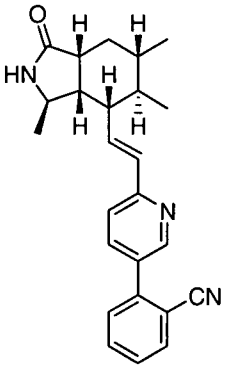
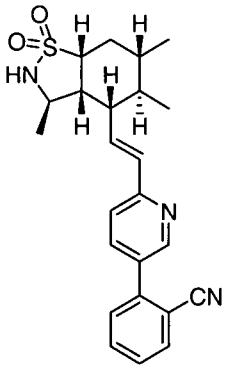
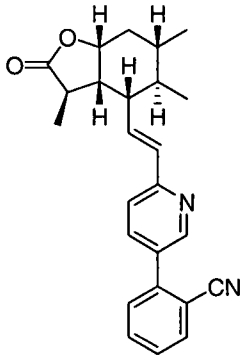
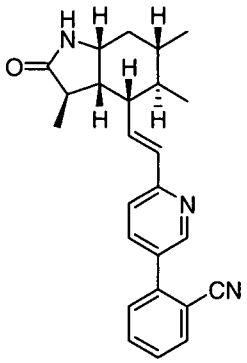
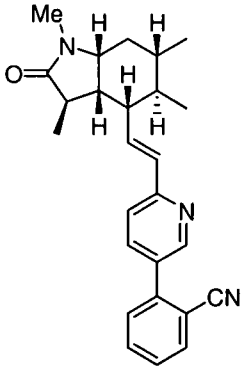
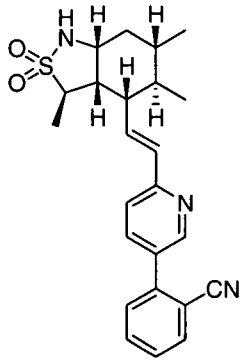
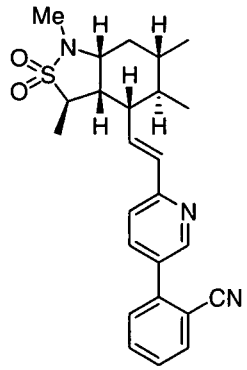




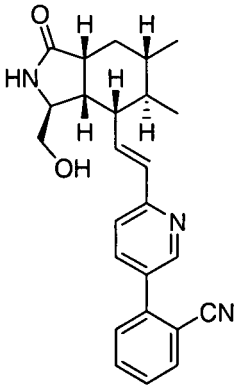
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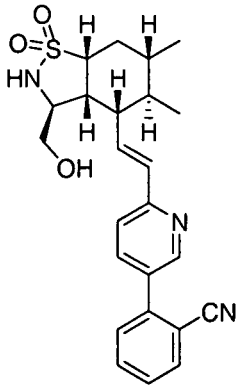


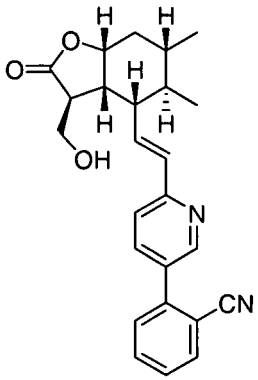
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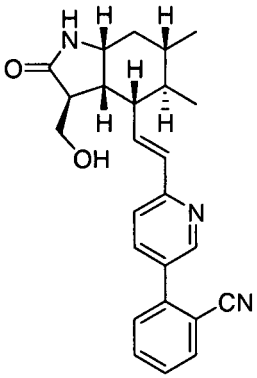








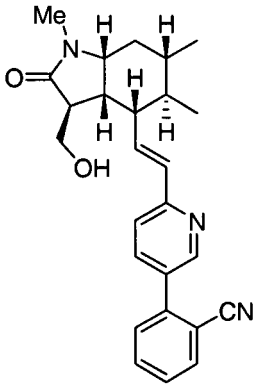
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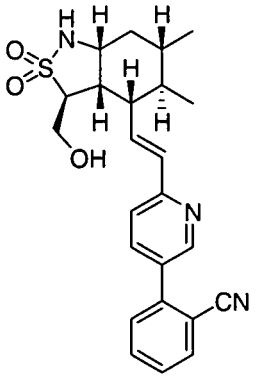


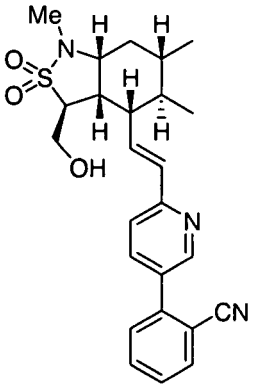


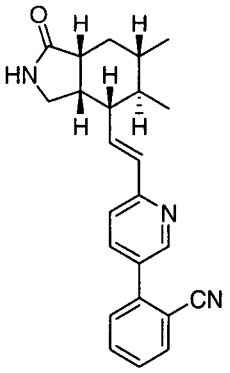


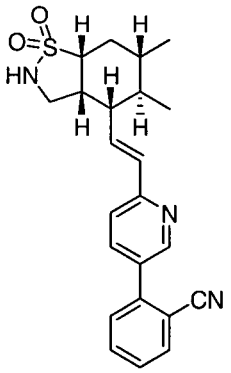


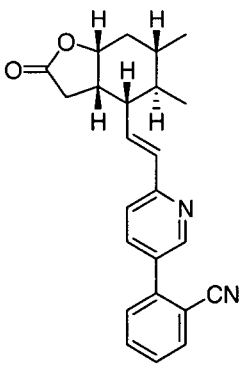


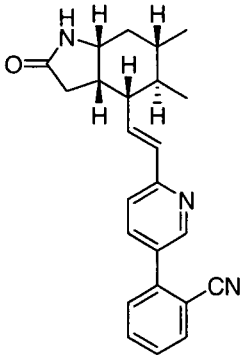


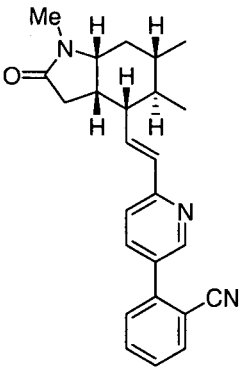


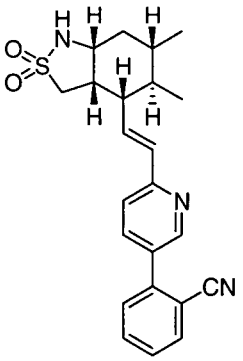


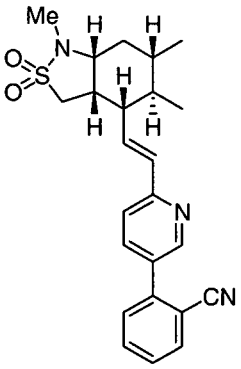


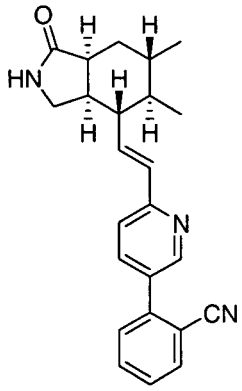


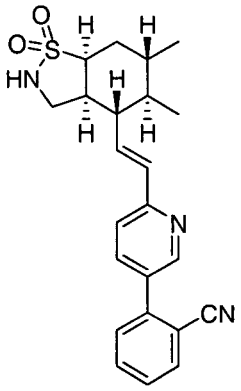


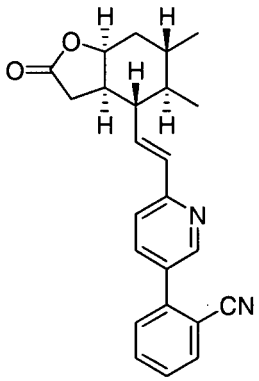


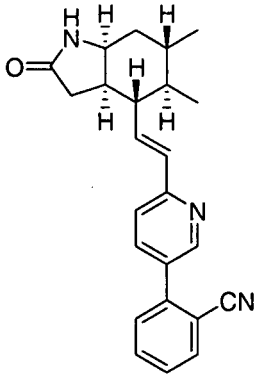


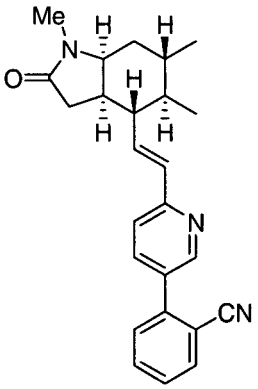


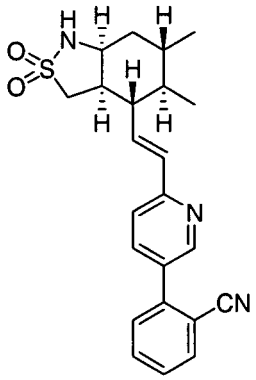


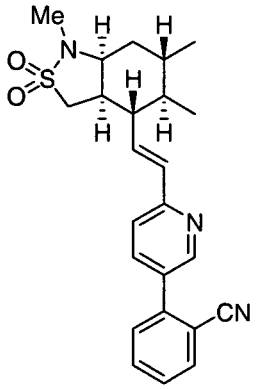


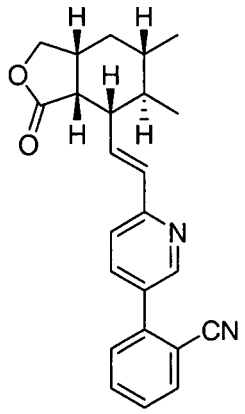


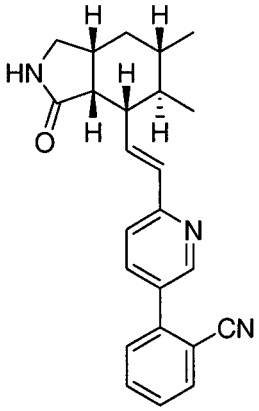


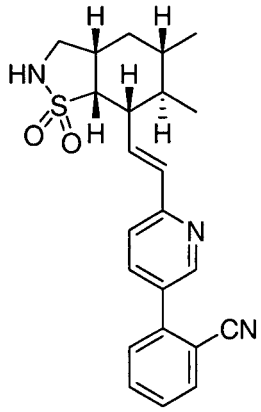


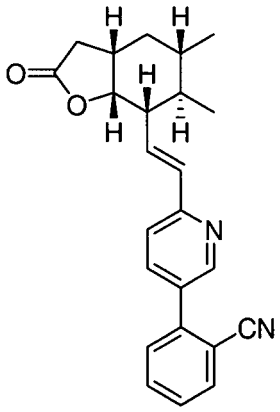


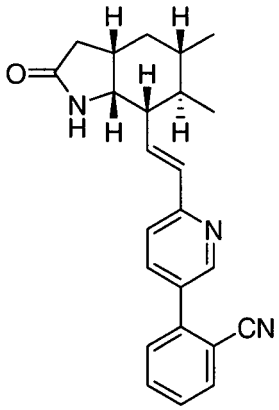


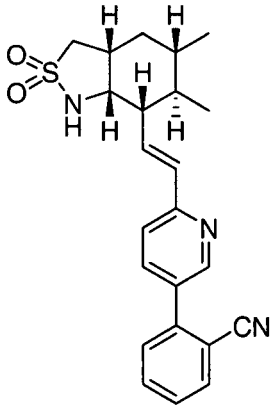


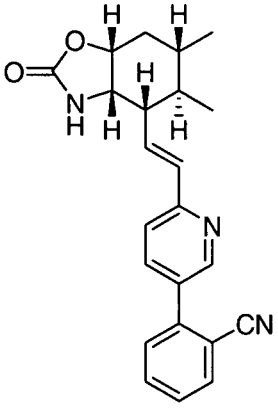


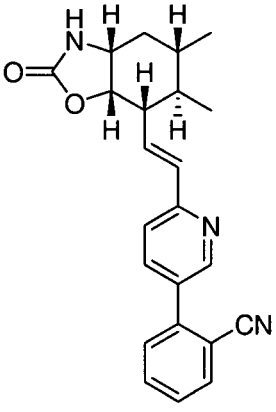


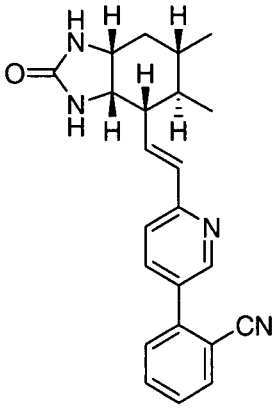


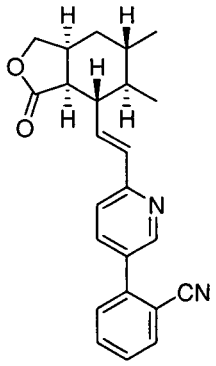


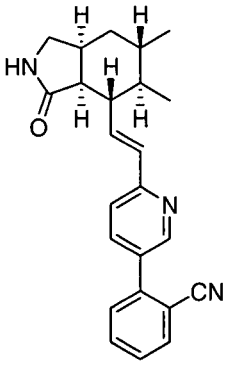


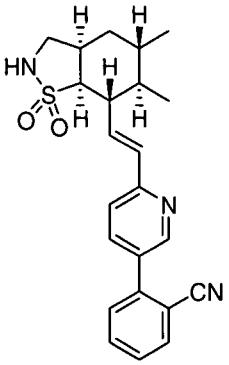


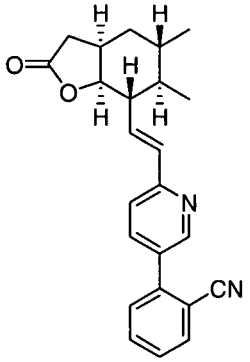


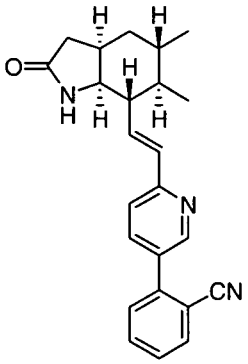


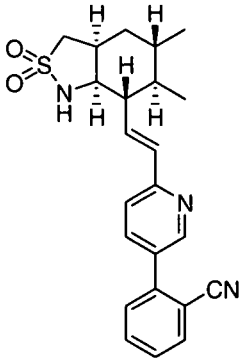


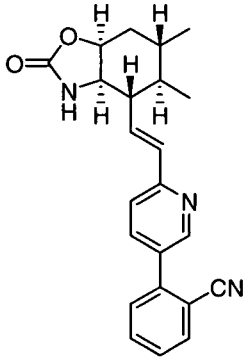


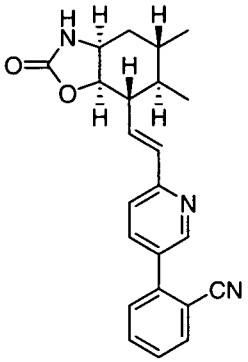


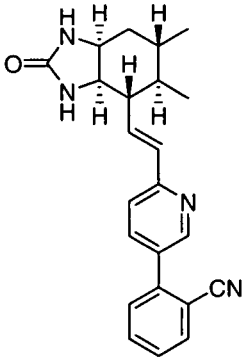




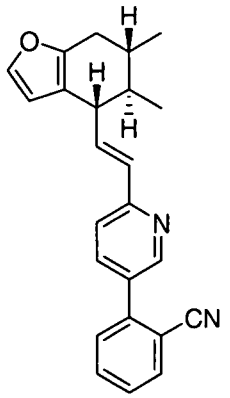
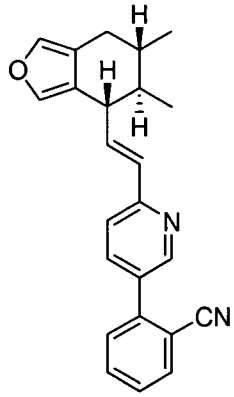
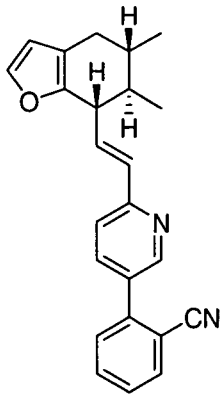
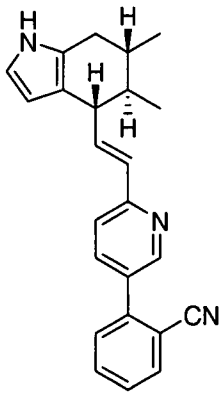
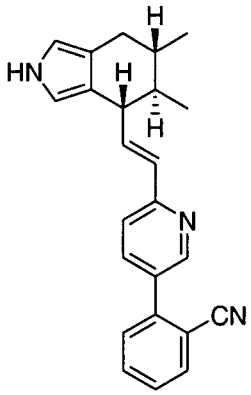
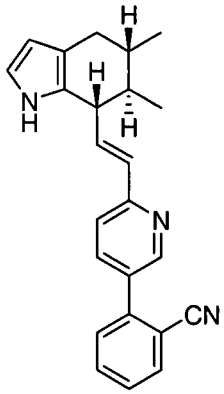
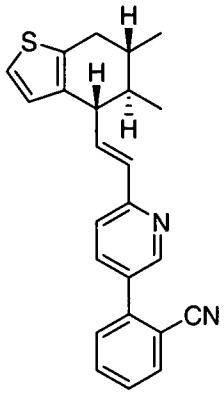
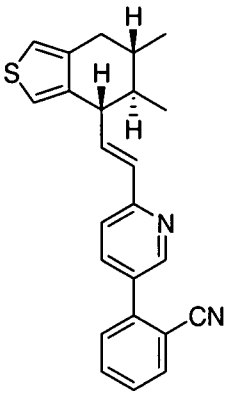
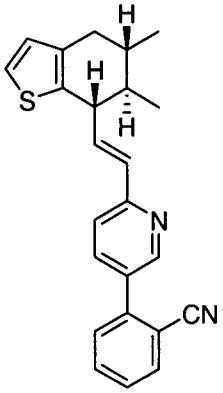


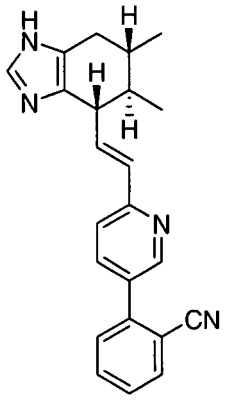


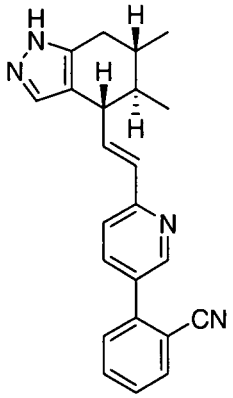


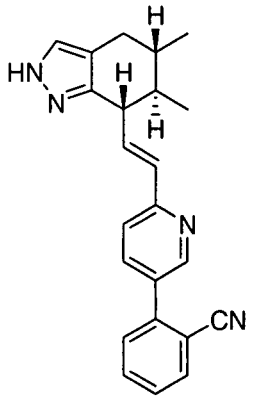


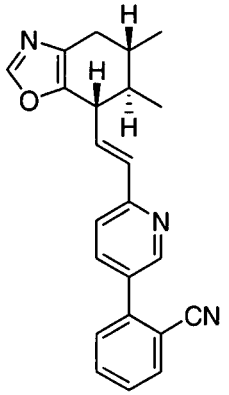
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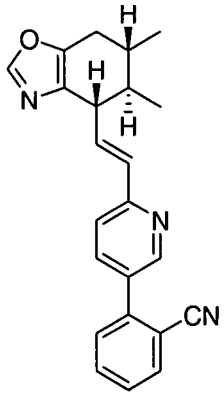










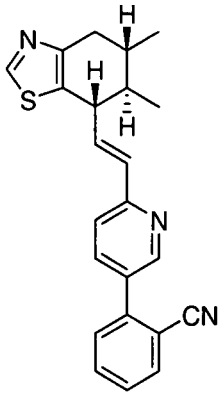


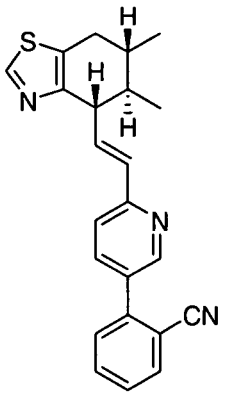




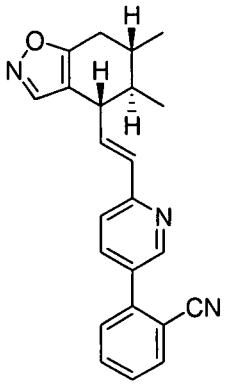


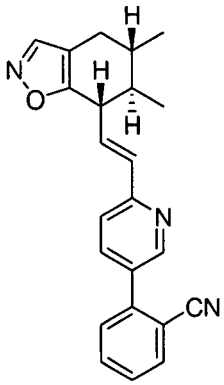


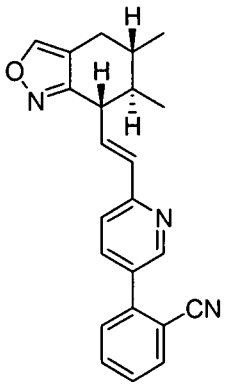


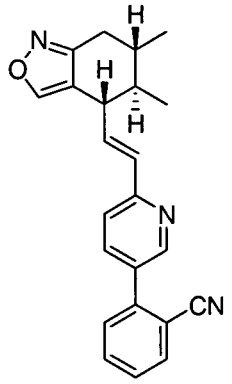


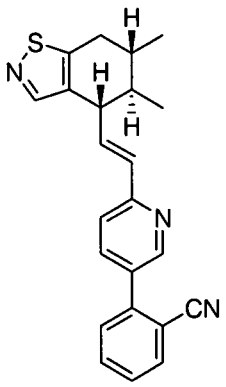
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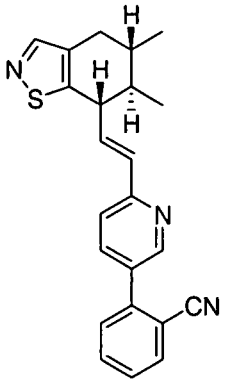


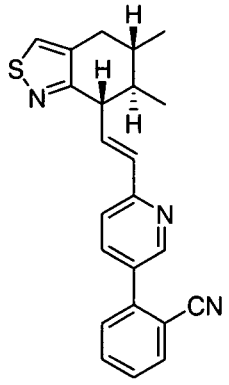


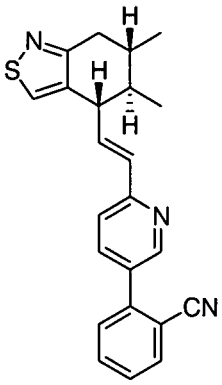






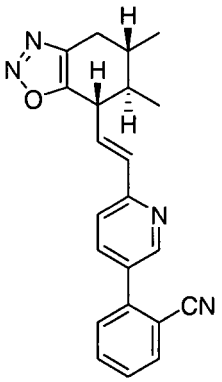


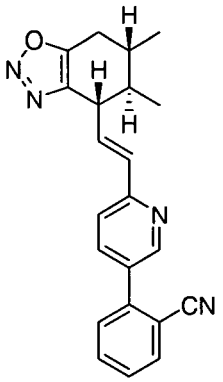


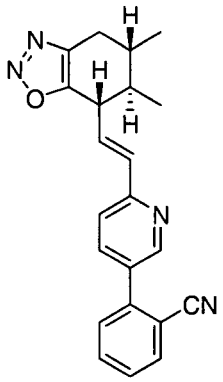


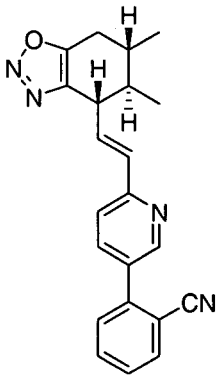
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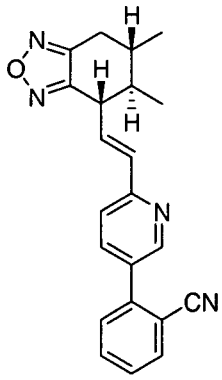
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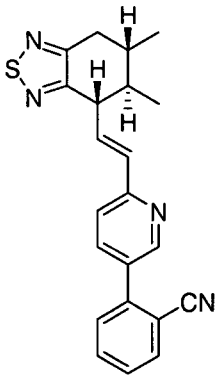


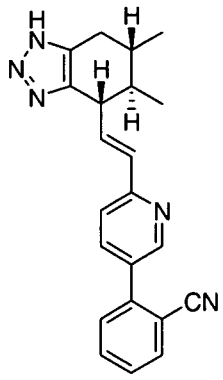




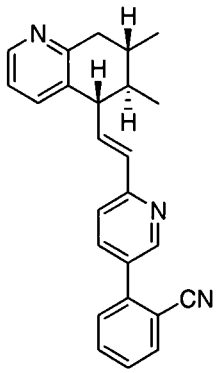


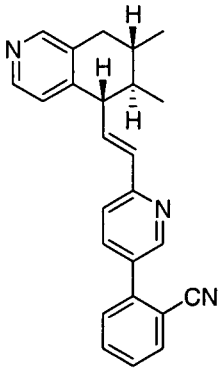


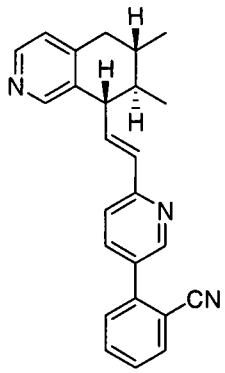


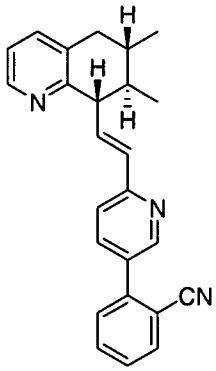


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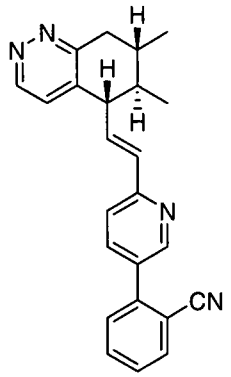


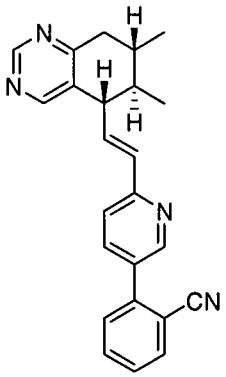


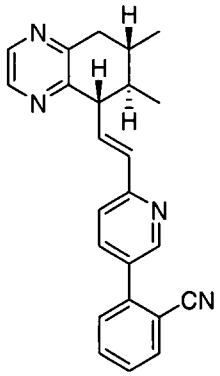


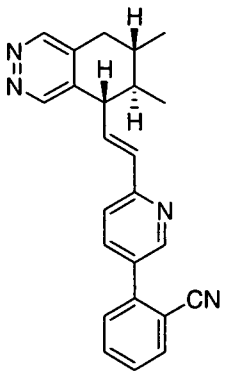


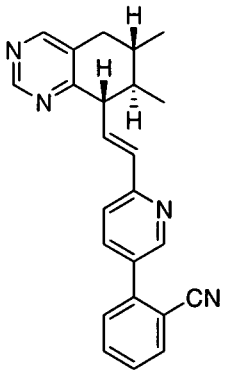
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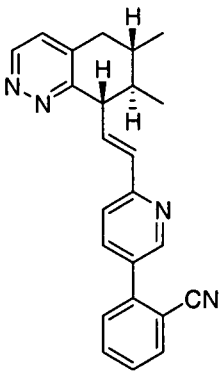


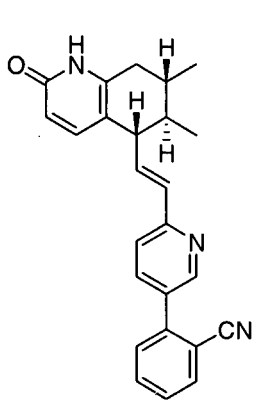


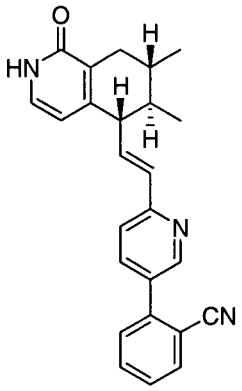


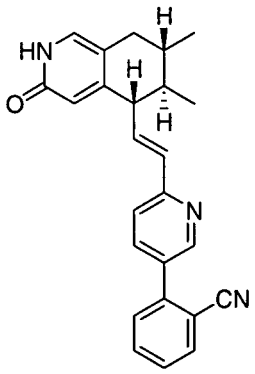


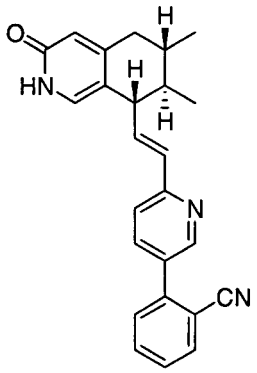




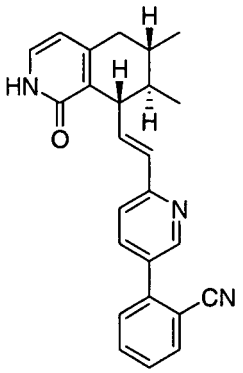








and



23. A pharmaceutical composition comprising an effective amount of at least one compound of claim 1 and a pharmaceutically acceptable carrier.

24. A method of inhibiting thrombin receptors comprising administering to a mammal in need of such treatment an effective amount of at least one compound of claim 1.

25. A method of treating thrombosis, atherosclerosis, restenosis, hypertension, angina pectoris, angiogenesis related disorders, arrhythmia, a cardiovascular or circulatory disease or condition, heart failure, acute coronary syndrome, myocardial infarction, glomerulonephritis, thrombotic stroke, thromboembolytic stroke, peripheral vascular diseases, deep vein thrombosis, venous thromboembolism, a cardiovascular disease associated with hormone replacement therapy, disseminated intravascular coagulation syndrome, cerebral infarction, migraine, erectile dysfunction, rheumatoid arthritis, rheumatism, astrogliosis, a fibrotic disorder of the liver, kidney, lung or

intestinal tract, systemic lupus erythematosus, multiple sclerosis, osteoporosis, renal disease, acute renal failure, chronic renal failure, renal vascular homeostasis, renal ischemia, bladder inflammation, diabetes, diabetic neuropathy, cerebral stroke, cerebral ischemia, nephritis, cancer, melanoma, renal cell carcinoma, neuropathy, malignant tumors, neurodegenerative and/or neurotoxic diseases, conditions or injuries, Alzheimer's disease, an inflammatory disease or condition, asthma, glaucoma, macular degeneration, psoriasis, endothelial dysfunction disorders of the liver, kidney or lung, inflammatory disorders of the lungs and gastrointestinal tract, respiratory tract disease or condition, radiation fibrosis, endothelial dysfunction, periodontal diseases or wounds, or a spinal cord injury, or a symptom or result thereof, comprising administering to a mammal in need of such treatment an effective amount of at least one compound of Claim 1.

26. The method of claim 25 wherein the inflammatory disease or condition is irritable bowel syndrome, Cohn's disease, nephritis or a radiation- or chemotherapy-induced proliferate or inflammatory disorder of the gastrointestinal tract, lung, urinary bladder, gastrointestinal tract or other organ.

27. The method of claim 25 wherein the respiratory tract disease or condition is reversible airway obstruction, asthma, chronic asthma, bronchitis or chronic airways disease.

28. The method of claim 25 wherein the cancer is renal cell carcinoma or an angiogenesis related disorder

29. The method of claim 25 wherein the neurodegenerative disease is Parkinson's disease, amyotropic lateral sclerosis, Alzheimer's disease, Huntington's disease or Wilson's disease.

30. The method of claim 25 further comprising administering at least two therapeutically effective agents.

31. A method of treating thrombosis, atherosclerosis, restenosis, hypertension, angina pectoris, angiogenesis related disorders, arrhythmia, a cardiovascular or

circulatory disease or condition, heart failure, acute coronary syndrome, myocardial infarction, glomerulonephritis, thrombotic stroke, thromboembolytic stroke, peripheral vascular diseases, deep vein thrombosis, venous thromboembolism, a cardiovascular disease associated with hormone replacement therapy, disseminated intravascular coagulation syndrome, cerebral infarction, migraine, erectile dysfunction, rheumatoid arthritis, rheumatism, astrogliosis, a fibrotic disorder of the liver, kidney, lung or intestinal tract, systemic lupus erythematosus, multiple sclerosis, osteoporosis, renal disease, acute renal failure, chronic renal failure, renal vascular homeostasis, renal ischemia, bladder inflammation, diabetes, diabetic neuropathy, cerebral stroke, cerebral ischemia, nephritis, cancer, melanoma, renal cell carcinoma, neuropathy, malignant tumors, neurodegenerative and/or neurotoxic diseases, conditions or injuries, Alzheimer's disease, an inflammatory disease or condition, asthma, glaucoma, macular degeneration, psoriasis, endothelial dysfunction disorders of the liver, kidney or lung, inflammatory disorders of the lungs and gastrointestinal tract, respiratory tract disease or condition, radiation fibrosis, endothelial dysfunction, periodontal diseases or wounds, or a spinal cord injury, or a symptom or result, comprising administering to a mammal in need of such treatment an effective amount of at least one compound of claim 1 in combination with at least one additional cardiovascular agent.

32. The method of claim 31 wherein the additional cardiovascular agent or agents is selected from the group consisting of thromboxane A2 biosynthesis inhibitors, GP IIb/IIIa antagonists, thromboxane antagonists, adenosine diphosphate inhibitors, cyclooxygenase inhibitors, angiotensin antagonists, endothelin antagonists, angiotensin converting enzyme inhibitors, neutral endopeptidase inhibitors, anticoagulants, diuretics, and platelet aggregation inhibitors.

33. The method of claim 32 wherein the additional cardiovascular agent or agents are selected from the group consisting of aspirin, cangrelor, clopidogrel bisulfate, prasugrel and fragmin.

34. The method of claim 33 wherein the additional cardiovascular agents are aspirin and clopidogrel bisulfate.

35. The method of claim 33 wherein the additional cardiovascular agents are aspirin and prasugrel.

36. A method of inhibiting cannabinoid receptors comprising administering to a mammal in need of such treatment an effective amount of at least one compound of Claim 1.

37. A compound of claim 1 in purified form.

38. A compound of claim 1 in isolated form.

39. A method of treating or preventing radiation- or chemical-induced toxicity in non-malignant tissue in a patient comprising administering a therapeutically effective amount of at least one compound of Claim 1.

40. The method of claim 39 wherein the radiation- and/or chemical-induced toxicity is one or more of intestinal fibrosis, pneumonitis, intestinal mucositis, oral mucositis, intestinal radiation syndrome, or pathophysiological manifestations of intestinal radiation exposure.

41. A method of reducing structural radiation injury in a patient that will be exposed, is concurrently exposed, or was exposed to radiation and/or chemical toxicity; reducing inflammation in a patient that will be exposed, is concurrently exposed, or was exposed to radiation and/or chemical toxicity; adverse tissue remodeling in a patient that will be exposed, is concurrently exposed, or was exposed to radiation and/or chemical toxicity; or reducing fibroproliferative tissue effects in a patient that will be exposed, is concurrently exposed, or was exposed to radiation and/or chemical toxicity, comprising administering a therapeutically effective amount of at least one compound of formula I.

42. A method of treating a cell proliferative disorder in a patient suffering therefrom comprising administering a therapeutically effective amount of at least one compound of formula I.

43. The method of claim 42 wherein the cell proliferative disorder is pancreatic cancer, glioma, ovarian cancer, colorectal cancer, colon cancer, breast cancer, prostate cancer, thyroid cancer, lung cancer, melanoma, or stomach cancer.

44. The method of claim 43 wherein the glioma is an anaplastic astrocytoma or a glioblastoma multiforme.